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Integrating Chemistry, Clinical Practice, and Pharmacoepidemiology From Molecule to Population

DeepScience

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Preface

The book is the result of a belief that the greatest contributions in the field of therapeutic science are made on the borders of areas that were traditionally separate. The book From Molecule to Population is devoted to the light shedding on the most important chain between the design of a drug molecule and its final effect on human populations.

This journey of integration we map in four. Our starting point is the molecular basis with the studies of innovative chemical synthesis and bioactive scaffolds. This then becomes personalized therapy in clinical practice, across the translational bridge, under clinical pharmacy and close pharmacovigilance of the safety of individual patients. Lastly, we use the population-level lens and apply the systems of pharmacoepidemiology and the real-world evidence of a drug to gain insights into the extensive use, benefits, and risks of a drug.

This book targets students, scholars, clinicians in the field of pharmaceutical sciences, medicinal chemistry, clinical pharmacy, and in the area of public health. It belongs to those who want to have a unified idea of how the properties of the molecules predetermine the clinical practice and how the personal results of the patients influence the overall knowledge of the population health.

Our long run objective is to make people more collaborative and holistic minded. With links between chemical structure and population-wide effect, we will be able to help in a future where quality patient care is replicated by a smooth flow between drug development, clinical application, and safety monitoring anywhere.

Dr. Atul R. Bendale,
Dr. Vasimkhan T. Pathan,
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Chapter 1: Clinical Pharmacy Practice and Pharmacovigilance: From Individual Prescriptions to Safer Patient Journeys

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ABSTRACT:

Pharmacotherapeutic agents and the individual drug safety can be seen at the bedside of the patient and cannot be quantified through the regulative offices. In this chapter, the author discusses how pharmacy has transformed into a product-based, reactive field to a patient-centred and safety-oriented field. Clinical pharmacist have taken center-stage in care teams and are no longer in the role of the prescription check, but serve to preempt risk via pattern recognition, therapeutic review, and real-time intervention. As a result of incorporating pharmacovigilance into daily clinical practice and putting patients stories at the centre, pharmacists can act as the first line of defence of safety issues, finding the sub-signs before it develops into a more glaring issue. Authentic safety is often unnoticed; it does not depend on dramatic episodes but on negative events, which do not appear. This proactive position is, however, challenged by the workflow pressures and the myth that safety is separate to patient care. The future of progress requires safety to be built into or become a part of the clinical practice fabric, which will inspire collective responsibility and consider patients as partners in their care. Finally, developing safer patient experiences is based on a long-term observation at the point of medication consumption, whereby each detail is a part of health and well-being.

Keywords: bedside pharmacovigilance, clinical pharmacy, patient safety, proactive risk management, medication therapy review, patient-centered care

Introduction:

1. Why Drug Safety Begins at the Bedside

Drug safety is not something that just starts in the regulatory offices. It is not something that comes out of reporting portals or from guideline documents. It starts much earlier than that. It starts at the bedside. This is where medicines get to know people. And that is when the safety issues were identified. Many drug safety failures are not regulatory failures. They are clinical ones. [1] A reaction that was not recognised in time. A dose that was technically correct, but inappropriate for this patient. A symptom that was considered a disease, related to one, while it was actually drug-induced. Usually, these failures do not involve bad intentions. They involve overwhelmed systems. Disconnected care and assumptions. [2]

On the bedside, drug safety has a different appearance. Drug safety is not something abstract. It is very much a personal thing, really. For example, a patient got dizzy after taking a new drug, while another patient stopped eating because she was so nauseated that the nausea never seemed to go away. A lab result just barely changes enough to cause concern, but not enough to set off alarm bells. Someone has to notice. And this is where the nature of the clinical pharmacist starts to change. Not as someone who merely checks prescriptions after they have been written. But as a person who foresees risk and thereby prevents harm from occurring. [3] A safety professional through and through whether or not the formal designation exists. Clinical pharmacists do not stand by when the adverse events become glaringly obvious. They are at the forefront of the earliest departure from normal. The first signals. The slight differences. I don't know. Something is not right in those moments. Such a job is not spectacular. It hardly ever gets written down. Yet it is significant in that it stops the problem from getting bigger. Prevention is, therefore, always invisible. [4] At the bedside, pharmacovigilance has nothing to do with carrying around forms or using scales of causality. It is about focus. About being in the right place at the right time. About reconciling the patient's words with the evidence in the chart. At times, it is upwards communication. Other times, it is the extra question when everyone else has already moved on. Drug safety emanates from here because this is the very place where harm can still be held at bay. When a patient leaves the ward with an unrecognized reaction, a safety issue becomes retrospective. Incident reports are made. Data is reviewed. Later, lessons are learned. Important yes. But too late. [5]

At the bedside, there is something else. An opportunity to intervene while it still matters. This is the reason clinical pharmacy cannot be totally product, focused. And this is the reason pharmacovigilance cannot be kept at arm's length from clinical care. Drug safety, at its most significant level, is where the drugs are actually used. In real time. With real consequences at the bedside.

Aspect	Traditional (Product-Focused) Pharmacy	Modern (patient-Focused) Clinical Pharmacy
Primary Role	Dispensing, technical accuracy	Clinical decision-making, risk management.
Location	Pharmacy department	Ward, clinic, ICU (bedside)
Safety Approach	Reactive (error correction)	Proactive (risk anticipation)
Key Activity	Verifying prescription details	Therapy review, pattern recognition, patient communication.
Outcome Measured	Accuracy of Dispensed Product	Prevention of harm, patient outcomes.

Table 1: Evolution of Pharmacy Practice. [6,7]

2. Clinical Pharmacy as a Safety-Critical Discipline

This shift in focus, summarized in Table 1, means that clinical decision making is much more than just verifying if a prescription is correctly written from a technical standpoint. The dose may be perfectly right according to the paper, but it might still be wrong for the patient you actually see. The kidney function may change. The weight of the body varies. The previous treatment cycles are important. Also, what happened last week matters, not only the labs of today. In wards, medicines are hardly ever single isolated interventions. They are part of a constantly changing clinical picture. Comorbidities overlap. New symptoms appear. Old ones disappear.

Clinical pharmacists get familiar with this clinical flow and learn to work through it. They modify, reevaluate, and sometimes resist. That is where safety begins to take shape. Drug therapy review has been around for many years. It is one of the tools used by clinical pharmacy for safe medication. [8] It may appear to be a straightforward thing, a chart reviewed, a list of drugs, doses, and frequency. However, medication review in the real world is the recognition of patterns. It is recognising any irregularities in a set of drugs. For example, a drug that is administered twice without reason or is the case, an interaction that seems insignificant but in reality, is quite serious. [9] A supportive medicine that the doctor did not instruct the patient to stop. These are not big and dramatic mistakes. They are slow risks. Such risks, if not dealt with, accumulate, and together they constitute a problem. [8,10] In fact, drug therapy review is often the first step where the pharmacist can identify/notice an adverse drug reaction that has not been documented yet. Also, it can be before the symptoms that escalate, or the laboratory results that crash, or the patient complains. What makes the pharmacist different in this situation is that he/she notices the timing, the difference between the mainstay therapy

and the patient reaction (response), and the sequence of events or the subtle mismatch between therapy and response. [11]

This kind of detection is not automated. It depends on attention.

Protocols play a significant role. They help keep the care consistent. They also make it less likely that different people do different things. However, they are not made with the intention of dealing with exceptions. And clinical care is always full of exceptions. A patient who does not tolerate the standard dose. Another who reacts earlier than expected. Someone whose response does not fit the grading scale. This is where clinical judgment takes precedence over protocol adherence. [12]

Clinical pharmacists are normally brought up with the idea of honouring guidelines, but not to blindly comply with them. They are taught to recognise the circumstances when they should challenge an order that is technically correct but clinically unsafe. This is not rebelliousness. It is care.

Making the decision can be tough sometimes. It may involve asking a senior clinician to think over his decision again. At other times, it may be necessary to write down a concern even if it does not turn into an event. However, these moments are the ones that set clinical pharmacy apart as a safety, critical discipline. In contrast with reactive safety systems, clinical pharmacy looks forward. [13] It concentrates on what might go wrong and not just on what has already gone wrong. This future, oriented attitude is the main differentiator of safety, critical roles as compared to supportive ones. However, a lot of this work is still invisible. When harm is avoided, there is no incident, no report, and just a patient who is able to continue therapy safely. Such silence is often misinterpreted as a lack of contribution. Actually, it is the sign of an effective safety intervention. Making the decision can be tough sometimes. It may involve asking a senior clinician to think over his decision again. At other times, it may be necessary to write down a concern even if it does not turn into an event. However, these moments are the ones that set clinical pharmacy apart as a safety, critical discipline. In contrast with reactive safety systems, clinical pharmacy looks forward. It concentrates on what might go wrong and not just on what has already gone wrong. [13,14]

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3. When Medicines Go Wrong: Understanding Real Clinical Risk

It is seldom the case that medicines going wrong is due to a single wrong decision. In fact, it is most commonly a result of a number of small decisions that come together quietly and gradually. [15] The moment the reaction is visible, it is already too late because the system has in the meantime, failed the patient in several ways. Usually, drug,

related problems are depicted as standalone occurrences like an adverse drug reaction, an interaction, or a dosing error. However, in reality, these problems are more appropriately considered as various system failures and not as individual events. [16] Such failures could be those of anticipation, communication, and, in some cases, attention.

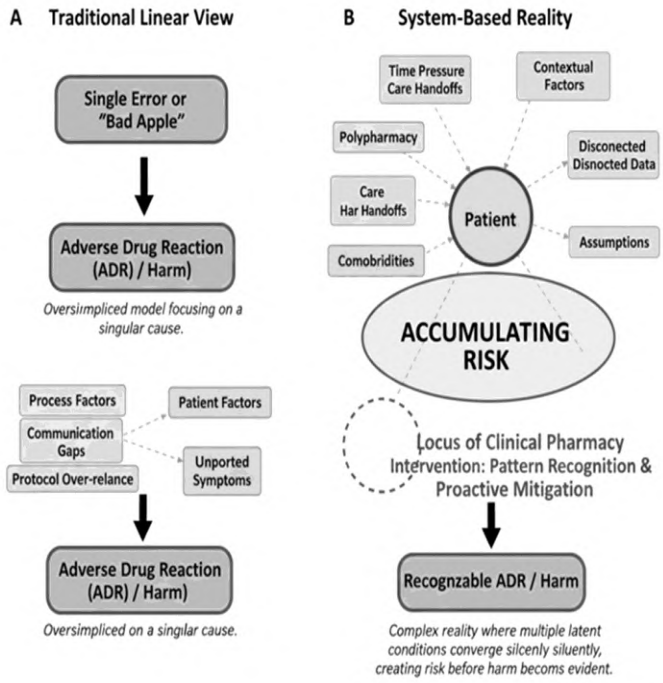

Fig 1: The Cascade of Clinical Risk: From Silent System Failures to Recognizable Harm.

During clinical postings, this pattern becomes hard to ignore.

Suppose a combination chemotherapy patient, and the regimen is standard. The doses are correctly calculated. Baseline investigations are normal. Everything seems okay. However, after therapy halfway through, the laboratory values start to change. The platelet counts drop more than predicted. The white blood cell counts take longer than usual to get back to normal. There is no bleeding. No fever. There is nothing urgent.

So nothing is done.

This is where risk is concealed.

Polypharmacy is a major factor contributing to the process. [17] Oncology patients hardly ever receive just one drug. They get several. Cytotoxic agents, antiemetics, steroids, analgesics, gastric protection, supplements. Each addition is justified when taken in isolation. Together, however, they create a level of complexity that is hard to predict by just referring to protocols. The adverse reaction doesn't present itself as an

emergency straight away. It comes gradually, and the symptoms become more prominent only when the therapy is reviewed over time. This is often where the system fails. Care is delivered in episodes. Patients come for treatment in cycles.

Decisions are continually revised, one cycle at a time. Unfortunately, no one really takes a moment to connect the dots between the present and the last cycle. Pharmacists with a clinical background are usually the ones who can come up with the solution for this gap. In case a patient experiences serious dextrin thrombocytopenic reactions to platinum, based chemotherapy, the case would be a predictable one. The situations that are known. Even, the cases, which are expected. Nevertheless, the expectation cannot be considered as a reduction of harm. The side effects of the therapy had not been properly foreseen. The adjustments of the doses were postponed. Monitoring thresholds were used to follow up on the situation after the damage had taken place and not to prevent it. The system did not fail because a drug was unsafe. It was a failure of the system, in which safety was considered as a matter of reaction, and not as something that could be proactively managed. [18]

Comorbidities complicate the picture even more. There is a considerable number of people, mostly elderly and patients who are taking high risk medicines, and for that reason, the patients' organs, such as the kidney and liver, are already compromised in function. Close to renal failure. Liver impairment. Poor nutritional condition. These elements do not very often directly cause deviation from protocols. Nevertheless, they increase the severity of drug toxicity when the patient is being treated. It is normal to be able to justify a slight increase in serum creatinine during chemotherapy. Problems with hydration. Old age. Heavy disease load. Sometime drug, induced nephrotoxicity, which is unfolding slowly, may be hidden. At the moment of intervention, the damage will be very serious.

Again, it is not a mistake of not noticing. It is the problem of structural vulnerability. [19,20] Vulnerable patients experience the greatest pain from the lack of support. Old people. Those with multiple health conditions. People who have difficulty diagnosing symptoms themselves. Individuals who think that discomfort is just the way treatment is and, therefore, do not complain. Their responses, in fact, are often quietly ignored in official statistics because they are normal in practice. Gastrointestinal toxicity is a textbook case. Continuous nausea, vomiting, or stomatitis might not qualify as severe ADRs. [21] Nevertheless, they hurt adherence, nutrition, and willingness to accept therapy. These results are of importance. However, they do not get acknowledged unless the right questions are asked.

Clinical pharmacists are the professionals most likely to pose those questions. One of these questions sounded like this: Do you ever feel sick to your stomach, throw up, or have really painful sores in your mouth? Which finally led her to a diagnosis of mucositis. From such experiences, a pattern emerges quite evidently. ADRs don't come

out of the blue. They are often the last stage of a series of ignored warnings. Unconnected, the signals existed but were overlooked. Lab findings taken only on their own. Symptoms are predetermined events without adequate questioning. Procedures are followed without any adjustments that are required.

It is common in the safety-critical fields that the story of failure is seldom dramatic; but it builds up. The traditional pharmacovigilance only records the final stage in the process: the reaction and the event itself. Clinical pharmacy on the other hand reverses the cause and effect to the point where the risk is actively established and thus intervention can change the outcome.

The perspective of adverse drug reactions (ADRs) as system failures changes the conversation and the focus is no longer on blaming others but on improving the process and the better monitoring techniques.
Earlier reviews. More deliberate dose reassessment. And most importantly, recognition that “expected” reactions still require management. Medicines do not fail patients alone. Systems fail patients by allowing harm to progress unnoticed. Clinical pharmacy exists to interrupt that progression. Not perfectly. Not always successfully. But consistently, and with intent. That is the real clinical risk. And that is where safety must be addressed. [21,22]

4. Pharmacovigilance Where It Actually Happens

Characteristic	Conventional/Regulatory PV	Integrated/Clinical PV
Primary Locus	National centres, databases	Bedside, ward rounds, patient conversation.
Trigger	Formal report of an event	Clinical observation, patient report, and lab trend
Temporal Focus	Retrospective (documenting past harm)	Real-time and prospective (preventing harm)
Key actors	Regulatory bodies, PV officers	Clinical pharmacists, patients, and frontline clinicians
Output	Aggregate safety data, signals	Immediate intervention, tailored care, shared knowledge

Table 2: Contrasting Pharmacovigilance Paradigms [23,24]

Most adverse drug reactions are probably recognised first by patients long before they are eventually reported. They show up as symptoms, changes in lab results, or slight deviations from the normal course of recovery. The patient feels more tired. The lab

result does not get back to the normal value. A patient's complaint is repeated through different shifts. These are clinical and not administrative moments. In wards, pharmacovigilance appears to be less formal. A talk at the rounds. A note in the chart. A question asked softly. Many times, it does not even seem like pharmacovigilance. It seems like regular patient care.

Drug reaction (ADR) identification is a very fragile process in outpatient departments as well. There is not enough time. The patients have a number of issues. Reactions that occurred at home are only vaguely described. "I was uncomfortable." "I couldn't tolerate it." These signs without a focused question are lost. The drug is continued. The risk continues. Different challenges are present in intensive care units. Here, the severity of illness masks the reactions. Many drugs are being constantly started and stopped. Organ dysfunction is frequent. It becomes difficult to distinguish disease progression from drug, induced harm. ADRs are not self, announcing clearly. They blend in. However, these are the situations where they really count. [25,26]

Clinical pharmacists assisting these patients develop an ability to identify patterns and not just events. They find that the timing of things is crucial. What was the impact of adding a drug? What changed after the drug was stopped? These are the kinds of observations that get done immediately. Even before a form gets opened. This is pharmacovigilance at its best. The difficulty arises in what happens next. No we mean what frequently does not happen. A side effect is found. The drug is changed or discontinued. The patient's condition has returned to normal. The problem that was there immediately has been taken care of. And that is the end of the story. No report. No documentation other than the standard notes. The incident fades away. One of the greatest failings of pharmacovigilance systems is this quiet disconnect between occurrence and reporting. [27] It is not from unawareness. Most healthcare professionals also know about reporting systems. It is from priorities. First comes acute care. Later comes the time for documentation. But often it is too late.

There is also some doubt, Was it really the drug? Maybe it was the disease? Was the reaction serious enough to report? These questions first of all create hesitation and secondly action is delayed. In busy settings, delay is omission. Clinical pharmacists, due to their training, are probably the only professionals who can comfortably handle this uncertainty. They are skilled in assessing causality of adverse drug reactions and can even decide whether a reaction should be documented when it eventually disappears. They know that pharmacovigilance includes not only recognizing the severe and rare events but also the whole picture: pattern, frequency, and context. Only through reporting will the visibility of these patterns be achieved. Another hindrance is the perception of pharmacovigilance. For many, pharmacovigilance is still a regulatory obligation rather than a clinical responsibility. A thing that is outside. Something that is extra. This results in a disconnect between daily practice and safety systems. Honestly, pharmacovigilance is very much a part of clinical care. It is there during ward rounds,

OPD follow, ups, and ICU monitoring. Paperwork comes second. First are the clinical observations. When clinical pharmacists combine pharmacovigilance with the habit of patient care, reporting turns out to be a natural continuation of practice, not an additional chore. It's not only the reaction that gets managed. It is registered. Shared. Added to the collective knowledge of drug safety. That shift, in fact, is the main event. [26,27,28]

Pharmacovigilance doesn't fail due to complicated forms. It fails because the events that get forgotten and unnoticed are allowed to end silently. At the bedside, in clinics, and in critical care units, safety signals are regularly generated. The challenge is not detection. It is a translation. From noticing to taking action. From acting to documenting. From documenting to learning. That's the point where pharmacovigilance actually takes place. Or not.

5. Integrating Pharmacovigilance into Daily Clinical Workflow

Pharmacovigilance can only really work if it's incorporated into everyday activities. If it is seen as an additional burden, people will invariably avoid it. If, however, it is perceived as a part of clinical work, it will be sustained. In fact, clinical pharmacists are the most common first responders to adverse drug reactions although they are not formally recognized as such. They are included during the ward rounds. They also do chart reviews before and after changes in prescriptions. They don't just check lab values in isolation, but in a sequence. This positioning is important. During ward rounds, the earliest safety signals are detected. A patient reports a symptom. A clinician observes a slow recovery. A dose is increased or another drug is added. These moments become cues for the pharmacist. Not to intervene immediately, but to monitor the situation more closely.

An adverse reaction does not necessarily have to be very visible to be significant. In this scenario, lab results become extremely important. Single numbers hardly ever carry any meaning. It's the changes that matter. A drop in hemoglobin over time. A late neutrophil recovery. A slow increase in creatinine. These scenarios are very often looked at separately by various team members. Usually, the pharmacist is connecting these signs to drug exposure. Graphs tell a different story. Starting dates. Stopping dates. Changes in doses. Supportive medications that last longer than planned. It is much easier to identify the risk when charts are reviewed together with labs and patients' complaints. Pharmacovigilance is embedded in the work process in this manner. Unobtrusively. Through connection. Usually, the pharmacist's reply to a suspected potential ADR is almost immediate but carefully thought through. Talk it over with the team. Propose tight watch. Suggest the dose should be changed. In some cases, it might be a good idea to temporarily stop the drug. All these interventions are mainly clinical decisions. The record comes afterwards.

And that order is significant. If pharmacists are to be made to put reporting above care, pharmacovigilance as a whole will fail. The main thing is always care. Reporting should

follow naturally from intervention and not compete with it. In various locations, clinical pharmacists are also translators. They change patient complaints into clinically meaningful information. They give explanations of drug, related risks in simple terms. They help teams decide whether a reaction is tolerable, manageable, or unacceptable. This function is even more important during transitions of care. Discharge is a very vulnerable moment. Medicines change. Monitoring is reduced. Patients are expected to be managing therapy on their own. Post, discharge reaction that becomes readmission is a very common scenario.

Pharmacists can facilitate patient safety beyond the hospital by incorporating pharmacovigilance with discharge counselling and follow, up planning. Even minor steps like counselling on warning signs or modifying supportive therapy may contribute to preventing the escalation. Eventually, these behaviours lead to a culture of vigilance. Staff members look forward to seeing pharmacists raise concerns. Pharmacists ask questions on a regular basis. The safety of drugs is not a limited discussion that accompanies emergency cases only.

This goal can be achieved not only by setting policies but by practicing it and trusting it. When pharmacovigilance is incorporated into the everyday routine of professional practice, it does not seem to be a distinct system and is part of delivering patient care. ADRs are detected earlier; they are intervened with immediately without postponement; their reporting becomes accurate by the virtue of a planned assessment as opposed to recalling past activities. Under this model, the pharmacist becomes not an observer but the first line responder of safety, which should take place before the harm is realized. It is an unfortunate fact that this working portrait of practical pharmacovigilance is not perfect or independent, but it is the modern reality of the business. [28,29].

6. Patient Centered Pharmacovigilance

Not all drug side effects can be confirmed through medical charts. Some are revealed only through patient feelings. Feeling of discomfort. Disruption of your daily routine. A symptom that seems too minor to warrant mention unless someone insists on it. In patient, centered pharmacovigilance, patients are not seen as mere recipients of therapy. They are considered sources of drug safety information. Most of the time, they are the ones who first realize that something is not right. Such a situation calls for trust. Adverse effects are not always reported by patients without being prompted. A great number of them believe that the reactions are normal and expected. Others are afraid that they will annoy the healthcare team if they report adverse effects. Some worry that if they complain about an issue, their treatment might be stopped. In the absence of reassurance, these adverse reactions remain hidden. [25]

Safety gap bridged by clinical pharmacists. Their interactions are not as rushed and more conversational, which enables the patient to be natural in their interactions. Formal assessments alone can never provide enough information as compared to informal patient inquiries. The term has not been discussed before, yet it is widespread. In this regard hearing is more than polite, it is a safety mechanism. In addition to symptom documentation, there is the need to assess the effects of medications on the usual functioning, including diet, rest, physical status, and willingness to go on with therapy. These aspects can be neglected during regular visits, but they have a strong effect on adherence and long-term safety of treatment. The most important element of communication is risk; better informed patients are more likely to report side effects. Understanding information makes it easier to eliminate fear and minimize under-reporting. Trust builds when the patients feel that their concerns are being addressed. [23].

Even minor changes are enough to create change: changing the time of dosing, choosing other therapies, or discussing the factors that cause the symptoms. These reactions give a substantial basis of a perceived rationality of reporting.

Patient-centred pharmacovigilance is not only limited to hospitals to the community. Numerous ADRs are post-discharge, as they are dealt with after monitoring and through restricted access to care. Lack of appropriate information might result in failure by patients to seek assistance or abandon treatment at short notice. Clinical pharmacists can be relatively helpful to counter the impact of this risk because they prepare patients to go home and discuss possible warning signs, when medical care is necessary, and to teach them to communicate openly instead of suffering in silence. Such conversations do not have to be based on advanced systems.

They need time and genuine care only. Where follow, up is possible, it makes the whole model even stronger. Minimal contacts are still sufficient to catch situations where a drug reaction is refusing to heal or issues that have arisen. People tend to talk more when they are at home with their families and not in the hospital ward. They are also more relaxed. [29]

Engaging patients in pharmacovigilance changes responsibility as well. Safety is a shared human value and shared effort. It is no longer something that is imposed on patients but something that patients and healthcare providers do together. This collaboration leads to better detection of and, most importantly, prevention of. However, patient, reported information loses its value if it is not taken seriously. If patients are told that their symptoms are minor or inevitable, this will discourage them from reporting in the future. Clinical pharmacists are instrumental in acknowledging patients' feelings and experiences and in communicating them to the care team to take necessary steps [25].

Patient, centered pharmacovigilance should not be viewed as a substitute for formal reporting systems, rather it is a complementary tool. It plugs the gaps that structured data are unable to cover. It communicates the direct experience of the patient with medication. In the end, the safety of the patient does not stop at discharge. The medicines go on. So do the effects. If patients are given the power to identify and report the harm, pharmacovigilance becomes an active part of normal life. This is actually the place where it has the greatest impact. [24,29]

7. Measuring the Impact of Clinical Pharmacy Interventions

The effect of clinical pharmacy is sometimes doubted because it is not that evident. If something goes wrong, it is clear. If something is prevented, it just disappears. No event. No alert. No headline. That is why measurement is an uncomfortable thing. Clinical pharmacy interventions are not usually accompanied by immediate, spectacular outcomes. On the contrary, they are the main reason for a gradual reduction in risk. They may shorten the period of recovery. They prevent the possible deterioration which did not actually happen. This kind of impact cannot be easily quantified by simple metrics. However, results are what matter. It is a well, known fact that one of the most direct effects of the pharmacist’s involvement is the decrease in the number of adverse drug reactions. Not doing away with the problem completely. Just the reduction. Less severe reactions. Identification at an earlier stage. Facilitating proper management. In the hospital wards where the pharmacists are actively engaged in reviewing the therapy and in attending the rounds, the severity of the adverse reactions is often lessened significantly as they are detected at a much earlier stage. Before escalation. Before ICU transfer. Before prolonged hospital stays. [6,14]

Drug errors are on the same wavelength. Tweaking the dosage, getting the physicians instructions clearer, and recognizing drug interactions are a few examples of the doctors work that hardly get recognized as interventions after the fact. Instead, they are the

everyday stuff. Nevertheless, in the long run, they restore the patients confidence in the system by supporting the line of defense that is within the medication process. From the systems perspective, it might seem that nothing has happened. For the patient, it is safety. Hospital admissions are yet another indicator of the story. A large number of hospitalisations related to drug use problems could have been avoided. Poor tolerance. Unchecked side effects. Discharge confusion. Whenever pharmacists take part in medication review and counselling, the number of readmissions due to medication, related issues usually goes down. Not completely. But significantly. [20]

Economic outcomes usually get a lot of attention, sometimes even too much. The cost savings are indeed real; however, in clinical pharmacy practice, these savings are hardly ever the main impetus. Shorter hospital stays. Fewer tests triggered by ADRs that could have been avoided. Less frequent use of rescue medications. These kinds of savings are very discreet; they are the side effects of safer treatments.

Quality of care is more difficult to measure, but at the same time, it is even easier to perceive. Patients who know their medicines tend to follow the medication schedule more strictly. Teams anticipating ADRs are quicker to react. Communication gets better. Confidence grows. These are minor changes, but they last. Measurement can also fail to capture some things of equal importance.

Pharmacists can't always have their recommendations accepted by the doctor, a pharmacist can't always prevent an ADR, and patient outcomes can't always be traced back to the one intervention given. Care is a collaborative effort amongst members of the clinical team. The impact is shared. Expecting clear, cut attribution is to oversimplify human working environments. Clinical pharmacy plays a role in safety alongside the rest of the system, not apart from it. [27]

Documentation plays an extremely important role in this. When interventions are consistently recorded, different aspects can be seen. Types of ADRs. High, risk drugs. Recurrent issues. This kind of data over time assists the quality improvement process. It guides the revision of clinical guidelines. It reinforces pharmacovigilance data. [9,14]

On the other hand, the desire to be able to quantify the effects should not be the only reason for doing the work of a clinical pharmacist. If pharmacists only focus their attention on things that can be measured, they might overlook some important aspects of their work. Dialogues, explanations to the patient, quick recognition of the problem, all these and more are hard to quantify, but they are a most important part of patient, centered care. [23] Anyway, the real benefit of clinical pharmacy practice is in medicine usage changes. Not a perfectly safe one, but a safer one. Not a strict one, but a more thoughtful one. Not a reactive one, but a responsive one.

Hence, success does not necessarily mean that there were no adverse events, rather that there was alertness, that the intervention happened at the right time, that patients felt that their wishes were taken into account, and that the staff expected and welcomed safety, related questions. [4,12]

8. Limitations, Barriers, and Missed Opportunities

However, clinical pharmacy-led pharmacovigilance has not been working under perfect conditions so far. It functions within real healthcare systems. Busy healthcare systems. Imperfect healthcare systems. And those systems limit what you can do.

Category	Specific Barriers
Workflow and Priority	Underreporting due to perceived solved problems, time constraints, and competing clinical demands.
Systemic and technical	Disconnected reporting platforms, double data entry, lack of integrated feedback loops.
Knowledge and perception	Variable training in causality assessment, viewing PV as a regulatory rather than clinical duty.
Patient-Related	Unreported symptoms (viewed as normal), communication challenges, and lack of post-discharge support.
Cultural	Safety is seen as an add-on task, not a shared responsibility embedded in daily workflow.

Table 3: Common Barriers to Effective Pharmacovigilance in Clinical Practice. [2,5,27]

Discharge still remains a very risky moment. Any ADRs detected during the admission have not been communicated properly is one of the causes that the follow, up is inconsistent at the community safety monitoring level which is quite weaker. Sometimes, a reaction that is easy to handle the first time maybe will be the cause of the readmission. There are also patient, related barriers to communication. Some patients do not express their symptoms very well. Some get used to the discomfort. Some forget the details. There are cultural aspects that influence the communication. When patients are not actively involved, important safety, related information is missing. It is worth noting that not every missed opportunity is apparent. Most of them are and only after the event that they will be realized.

The reaction that became more serious; and the pattern of events that was noticed too late. These cases point more to system failings than to individual failings. [16] Recognizing the limitations of a system does not lessen the role of clinical pharmacy. It pinpoints the areas that need to be improved. Pharmacovigilance cannot be based on mere goodwill. It is dependent on time, an established framework, feedback, and the backing of the administration.

In the absence of these, safety remains a reactive measure. The problem is not that people fail to realize the significance of pharmacovigilance. The majority of healthcare workers are already aware of that. The problem is to keep that awareness when there are so many other demands on the practitioners' time. Also, to make sure that the safety measures are given their due even when, apparently, nothing goes wrong. That is still the point where a lot of chances are being lost. [5,18]

9. The Way Forward

Improving drug safety should not be equated with the need to create an entirely new field of pharmacovigilance. It is rather about changing its position. Pharmacovigilance needs to be brought closer to care, patients, and the professionals who are the first to see risks happening in real time. The progress for clinical pharmacy lies in acknowledging safety as one of the essential functions instead of being a spare time work. Pharmacovigilance cannot be a separate entity from clinical practice. On the contrary, it should be based on it. If safety consciousness is an integral part of daily clinical decisions, then reporting is simply another way of care rather than a bureaucratic task.

Education is the weapon here. Clinical pharmacy education has to go beyond mere knowledge gathering and deliberately put the spotlight on safety consciousness. How to identify risk. How to coexist with uncertainty. How to trace and document events even in cases of positive outcomes. Such skills are the result of training, self, study and guidance from seniors rather than lectures only. [1,16,24]

Although digital tools may provide certain advantages, they alone are not the answer. Decision support systems, reporting platforms that are integrated and electronic alerts can definitely promote vigilance. They can help to avoid doing the same thing twice. They can also enhance capturing of the data. But if there is no clinical judgment, they are still very crude tools. The purpose of technology is to aid observation, not to take over it. Additionally, there is a need for more intelligent reporting systems. They should be systems that fit naturally into the clinical workflow. Systems that give feedback. The more the clinicians are able to track how the reported data has been changed, the more their engagement increases. Pharmacovigilance becomes meaningful once again. [5,14]
Perhaps the most significant change is cultural. The safety has to be perceived as a work that is shared/ together. It shouldnt be one profession's work. Pharmacy clinicians are in an excellent position to bring about this change, but they cannot do it individually. Collaborating with physicians, nurses, and patients is vital. Drug safety becomes better when the conversation is a routine and the questions are welcomed.
Care for the patient has to be patient, not only within the hospital but also outside the hospital. By counselling, follow, up, and clear communication, pharmacovigilance can be seamlessly integrated into daily life. Patients who know their drugs well are very safe participants in the An example of how the partnership can be more effective in minimizing harm than technology is the drug safety process. [23,24].
The future of the pharmacovigilance is not in the new forms or higher regulations but in compliance: collecting the available knowledge, noticing the first indications, and response before it is too late. [16].
The intersections that have always been the subject of clinical pharmacy use represent protocol versus patient, data versus judgment, action versus prevention. This role is not quite a revolution but a logical extension. The most crucial precaution of drug is at the point of consumption; the difficulty is to be alert at that crossroad. [3,7].

Conclusion

The use of safer medication has less to do with perfect systems and more to do with human centred care that meets patient needs in a bedside. In this chapter, the change of the current state of clinical pharmacy and pharmacovigilance as administrative work into daily prevention-based activities is outlined. The nature of the pharmacist changes to be one of anticipation, collaboration, and just-in-time intervention by changing the pharmacist paradigm, moving off the reactive and product-focused model, and into a proactive model that is patient-centred. True safety is found in everyday actions: noticing trends, truly listening to patients, and asking the critical questions before any harm arises. It's about integrating pharmacists into healthcare teams, allowing them to respond to early warning signs and navigate the complexities of care. Success relies on fostering a culture where safety is a mutual responsibility, where reporting incidents becomes a

natural part of care, and where patients are treated as partners in their own healing processes.

While challenges like workflow pressures and underreporting remain, the way forward is evident. By embedding vigilance into daily clinical practices, aligning observation, action, and learning, we can create a healthcare system where safety is an intrinsic part of every interaction, leading to more secure patient journeys built on compassionate, consistent engagement.

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Chapter 2: Title-Emerging Trends in Personalized Medicine and Translational Therapeutics

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Abstract

Personalized medicine is a paradigm shift in medical practice whereby medical interventions can be applied to each person depending on their specifics such as genetics, environment, and lifestyle. This change in a standardized model toward a personalized one has significant potential and can lead to a better patient outcome, better treatment compliance, and decreased adverse outcomes. The identification of biomarkers and targets of treatment are enabled by the advancements in genomics, proteomics, and the analysis of data, which result in the design of individual diagnostics and treatments in numerous medical disciplines. Nevertheless, the universalization of personalized medicine is presented by such problems as the privacy of information, regulatory barriers, and the aspect of innovative technologies. The article summarizes, morality, technological progress, medical application, challenges and prospects of personalized medicines. This is a medical paradigm that involves unique, regular, participatory and predictive practices. It will also enhance effectiveness of treatment through identification of genetic factors that are behind the sickness of an individual. It has the potential to reduce time expenses, as well as improving the quality of patient's life. It is a strategy that can help in enhancing the efficacy of treatment since the genomic constitution that causes diseases in a person is determined. Individualized medicine has numerous uses and it can be applied in the diagnosis of different diseases.

Keywords: Personalized medicine, Heath care, Genome, Diagnosis, Target therapy

1. Introduction

Personalized medicine represents a revolutionary development in medicine as it leaves the standardized practices behind in favor of personalized medicine. It recognizes the importance of genetic makeup, lifestyle and environmental influences into health and responsiveness to treatment [1]. Personalized medicine, based on the application of modern technologies: genomics and data analytics is expected to be an innovative approach to healthcare delivery, bringing specific and personalized treatment [2].Personalized medicine is based on an intensive study of the genetic makeup of genomic sequencing. The clinicians will be capable of determining specific genetic variations and mutations, which influence on the susceptibility to the disease, drug metabolism and drug reaction, treatment plan towards individual patients and improving success and decreasing the number of side effects. Implementation of personalized medicine in the 21st century can only be effectively achieved when there are effective diagnostic measures, which will help in the selection of the most appropriate therapeutic product to the different patients, to enhance patient outcome [3].Manufacturers and Food and Drug Administration thoroughly control such products [4].

Personalized medicine has potential in many aspects of healthcare. It enhances the level of diagnostic since it is able to detect the genetic pointers that are linked to some diseases, and therefore, it is able to intervene at an earlier stage and attain improved outcomes. Furthermore, it also facilitates the process of individually tailored treatment and results in maximum therapeutic efficacy and happier patients as their genetic tendency and risk factors are recognized, enabling them to choose a particular approach to prevent the disease[5].More than that, it simplifies the treatment process, which maximizes its therapeutic value and makes patients happier[5]. One of the simplest characteristics of personalized medicine is genomic sequencing which makes it possible to study the genetic map of an individual in detail. Drug metabolism, genetic differences, and mutations as a risk of disease identification Healthcare providers can design interventions to fit the genetic profile of a particular patient by identifying the genetic variations and mutation and how the two relate to each person. Such an individual approach proves to be tremendously promising in a variety of healthcare areas:

- Precise diagnosis: Personalized medicine allows timely and more precise diagnosis of a particular disease through the identification of genetic markers and molecular patterns that can be associated with that disease resulting in more specific and effective therapy [6].
- Individualized Therapy: Personalized medicine allows the choice of the treatment that is more likely to be effective in the person and minimizes the possibility of overdose or resistant treatment. This may give rise to improved results and increased quality of life of patients [7].

• Preventive Care: through the assessment of the genetic tendencies and risk factors of an individual, personalized medicine enables the development of personalized prevention plans. These include lifestyle change, screening plans, and early preventive measures to reduce risk of diseases and enhance well being[8].

• Clinical Research: Customized medicine is also promoting innovation in clinical research, which makes it easier to develop new therapies and interventions that address a particular genetic variation or molecular pathway. Such a plan can speed up the process of medical discoveries and make it faster to bring new treatment to the market [9].

Although personalized medicine has achieved much over the last few years, there are still certain problems as far as the access to genetic testing, issues about the privacy of the data and the lack of integration of personalized medicine into the routine clinical practice. Nonetheless, personalized medicine is on the verge of revolutionizing healthcare delivery and improving patient outcomes globally with on-going technological growth and more awareness among the healthcare professionals and the patients.

Personalized medicine is a new field of medical practice that applies genetic data of an individual to make decision-making on disease prevention, diagnosis and treatment. Knowledge of the genetic composition of a patient will help a doctor prescribe the right drug or treatment and use it at the right dosage or the right time. The data on such programs as the Human Genome Project [10] are used to develop a customized medicine. Various stakeholders of healthcare such as physicians, healthcare administrators, insurers, and, finally, patients are involved in the adoption of personalized medicine [11].

Personalized Medicine: A Brief Overview

Personalized medicine refers to a form of medical treatment and prevention, in which individual difference in medical treatment, environment, and lifestyle is taken into consideration on the foundation of individual differences in genes. Rather than the one-size-fits-all approach used in the past, personalized medicine is the concept that seeks to address the unique features of each patient[12].

Mode of working:

Table No.1 Mode of Working of Personalized Medicine

Component	Description
Genetic Information	Interpretation of the genetic make-up of a person to determine his or her susceptibility to diseases and also determine how an individual responds to treatment by means of genetic tests and the determination of gene variations[13].
Individualized Treatment Plans	Application of genetic and clinical information to construct patient-targeted treatment plans that are safer and more effective than conventional treatments (e.g. targeted cancer therapies)[14].
Preventive Strategies	Determination of genetic and lifestyle risk factors to be used to carry out customized preventive interventions to minimize the onset of disease or its progression [15].
Monitoring and Adjustment	Constant check-ups based on the biomarkers, genetic tests, and diagnostic measures to measure the effectiveness of the treatment and adjust it in due time [16].

In sum, the concept of personalized medicine can transform the medical field in multiple aspects, offering more accurate and efficient treatment, benefiting the patient, and saving on health care expenses by preventing useless or unnecessary care. Nonetheless, there are still obstacles in regard to access to genetic testing, the issue of privacy of data, and the fact that medical professionals may lack the training and resources to apply personalized medicine methods successfully. Personalized medicine is a developing discipline where clinicians apply diagnostic tests to identify medical interventions that would be the most effective in treating individual patients or involve manipulating of molecular processes that affect health using medical interventions. Personalized medicine refers to the development of specific prevention and treatment plans with their patients through the combination of diagnostic testing data and the individual medical history, circumstances and values of the individual patient [12]. It is based on the scientific discoveries in the knowledge of how unique molecular and genetic profile of a particular person predisposes him to some kind of disease. The same

study is making us more able to forecast, which type of medical treatment will be safe and effective on each patient. Personalized medicine viewed as a continuation of the conventional methods of disease knowledge and treatment. Installed with tools that are more accurate, physicians can choose a therapy or treatment protocol that not only can reduce adverse side effects and increase the likelihood of a successful result, but can also assist to regulate the expenses in the case of treating the disease with a trial and error approach [17]. Personalized medicine can transform the manner in which we conceptualize, diagnose and treat health issues. It has already been having an exciting effect on the clinical research as well as patient care and this effect will continue to increase with the improvement of our understanding and technologies [18].

Challenges:

The challenge concept of Personalized medicine is identified as a new contribution to the healthcare system by its focus on prevention, coordination, and its effectiveness[19,20].Although the benefits of personalized medicine are evident, the stakeholders and consumers have not fully realized the benefits of the existing healthcare system. Recent studies also point out some of the barriers to the development of personalized medicine which includes scientific obstacles like how to establish the clinical value of genetic markers and lack of knowledge about the molecular pathogenesis of a certain disease [21].There are also economic barriers; there is also the complexities involved in operations when it comes to identifying technologies and systems of operation that would save them money [22]. Furthermore, the issue of safe protection of private information throughout the investigation and development stages is still of concern. Issues of policy dilemma also make matters more complicated, especially in regard to the liaison between government research institutions and government regulatory agencies [23].

Although personalized medicine has tremendous potential in customizing medicine to suit a particular patient considering their unique genetic composition, lifestyle habits and environment, there are a number of issues that need to be overcome:

Data Privacy and Security: Personalized medicine works on the assumptions that it involves the collection and examination of sensitive and patient data, including genetic data. This data is relevant to the privacy and security of the data and is vital in patient compliance and trust [24].

Cost: It is possible that it is too expensive to create individualized treatment, which needs complex diagnostics and genetic screening and special treatment. The cost of these treatments may limit its provision particularly to individuals who do not have the appropriate insurance cover [25].

Ethical Implications: There are ethical concerns in individualized medicine; the use of genetic information to make decisions and potential discrimination of individuals with genetic weaknesses and equitable distribution of resources[26].

Regulatory Hurdles: The issue of regulatory bodies should lay down the ground-rules to authorize and regulate personalized treatments is one of the problems that they must tackle given the need to foster innovation,patient safety and efficacy [27].

Interdisciplinary Collaboration: The application of personalized medicine will demand the collaboration of healthcare providers and researchers, policymakers and technology experts to work together. Intermediation between these fields might not be very easy but this will be required to boost developments in the field [28].

Health Inequities: There are chances that personalized medicine will contribute to the health inequities that already exist provided that access to the most recent treatment is unevenly distributed across certain groups of people or geographical locations [29].

Data Interpretation: The massive amount of data generated in the context of personalized medicine is a large task to interpret.Combination of genetic, clinical, and environmental data to make actionable treatments is a complex computational and analytical task [30].

Patient Education and Engagement: To provide patients with the opportunity to make the right choice in the context of individual treatment, they need to be informed about the benefits and risks of genetic tests and personalized medicines and their shortcomings [31].

It will be necessary to address these challenges to achieve the maximum potential of personalized medicine and make sure that it is beneficial to patients of different populations. These barriers can be overcome through collaboration, innovation, and adherence to ethical standards, which will help develop the sphere of personalized medicine.

Benefit to patients:

Personalized medicine may entail either preventive, diagnostic or treatment approaches.

- **Prevention**
  Preventive personalized medicine is aimed at assisting patients to have the knowledge of their molecular and environmental disease risk.
- **Diagnosis** Diagnostic tests have the potential of revealing the underlying molecular mechanisms of some diseases. The findings can lead to an effective targeted treatment therapy, which would have been neglected otherwise [32].Treatment Individualized medicines would be able to treat the fundamental cause of some illnesses on the molecular level. Molecularly targeted therapy regimens are safer and more effective to a great number of patients compared with one-sizes-fits-all [18].
- **Targeted Treatments:** Personalized medicine is genetic, environmental and lifestyle-based treatment that is used to determine the best treatment in a specific individual. The implication of this is that there is likelihood of more effective treatments since these treatments are properly selected according to the individual biological makeup of the patient.
- **Minimized Adverse Effects:** Personalized medicine will minimize adverse effects by taking into account the individual differences. Treatments and drugs are selected based on a more informed understanding of how a patient will react to it minimizing the chances of adverse side effects.
- **Individualized dosages:** Individualized medicine can also be used, i.e., whereby one of the patients has his/her dosage of the medication according to his/her genetic composition, metabolism rate, and other individual factors. This is capable of maximizing efficacy of treatment with the least possibility of under or overdosing.
- **Cost-Effectiveness:** despite the high diagnostic and treatment methods and interventions associated with personalized medicine, it may end up being cost-efficient by preventing unwarranted care, lowering hospitalization, and enhancing efficiency in the overall healthcare system [33].

Innovations:

The FDA is also occupied in designing and testing animals models to find out the safety and efficiency of the bacteriophage cocktails to treat bacterial infections that are classified as antibacterial resistant. Invention and implementation of pharmacogenetic tests and gene therapies are other impacts. These tests will provide the clinicians with the data of the response of the genetic background of

the individual to a particular treatment. In addition, The FDA scientists are also involved in the critical regulatory science matters that relate to the approval of drugs, particularly the modes of using immunotherapy agents and new methods of treating various types of cancers. They are also addressing the problem of genetics in the evolution of immune-related adverse effects and the response to such agents [34]. The FDA has detailed its efforts in January 2021 in letting clinicians know the advancement of therapeutic methods development as the role of personalized medicine is increasing. The FDA has developed a draft of submissions of investigational new drugs of individualized antisense oligonucleotide (ASO) product, which are supposed to treat a severely debilitating or life-threatening genetic disease [31, 35].The following guidelines: The approach to receiving the FDA with a well-developed communication scheme the anticipations and the process of making the regulatory submissions to the FDA; and the suggestions regarding the status to be granted to the protocols by the Institutional Review Board in the review of the protocols and how to take the informed consent.

Personalized medicine application The following are some notable uses of personalized medicine:

1. Earlier detection of diseases in their early development stages by optimized surveillance which gives a chance to develop more effective interventions or options of treatment.
2. Reducing the number of preventable complications and side effects of using drugs due to the practice of generic one size fits all prescribing.
3. Maximizing therapeutic efficacy, through the provision of the right drug and any genetic differences that might affect the metabolism of the drug when prescribing the drug regimen.
4. Helping people who have a high risk of contracting diseases by encouraging and aiding compliance with the existing prevention measures.
5. Genetic Testing: Genetic tests are able to detect the inherited predispositions to some diseases and hence, early intervention or prevention. As an example, BRCA gene testing can be used to identify the risk of breast and ovarian cancer, which would then be used to develop a personalized screening and treatment strategy[36].
6.Oncology Cancer Treatment: Personalized medicine Oncology is the study of genetic make-up of tumor that identifies specific mutations that help in the increase of cancerous growth.This fact aids oncologists to choose targeted

therapies that would be more effective and less side-effects than the conventional chemotherapy[37].

7. Pharmacogenomics: Pharmacogenomic is a test that investigates the effect of the genetic composition of an individual on how much it reacts to drugs. This knowledge will assist health care providers to prescribe the most appropriate medications and drug dosages, which reduce adverse reactions and maximize the efficacy of treatment [38].

8. Infectious disease Management: Personalized medicine is starting to find application in the management of infectious diseases, including HIV and hepatitis C. Genetic testing is used to identify individual patients with the most effective antiviral drugs and consider factors such as drug resistance mutations and host genetics [39].

9. Rare disease: Personalized medicine is a notion that has a potential to bear fruits in a person who has a rare genetic disorder since personalized treatment of an individual based on his/her genetic mutations can be introduced. The strategy can improve treatment and quality of life patients with conditions, which have limited therapeutics option [40].

10. Preventive Medicine: Under the knowledge of the genetic predisposition of an individual to a given disease, personalized medicine may be applied to prevent these diseases by lifestyle modification and early diagnosis to reduce the risk of constricting chronic diseases such as cardiovascular disease and diabetes 41].

11. Patient Stratification in Clinical Trials: Personalized medicine increases the effectiveness of clinical trials as it is possible to determine patient subgroups with the greatest likelihood of responding to experimental treatments. This system will help to come up with new therapies that have a better efficacy and safety profile, resulting in more effective clinical outcomes [42].

12.Behavioral Health and Psychiatry: There is a growing interest in the application of genetic testing and personalized medicine to psychiatry and behavioral health to maximize the choice of psychotropic drugs and improve the outcome of the treatment of depression, anxiety, and schizophrenia[43].

Benefits of personalized medicine.

- Enhance benefits to the healthcare systems and the society.
- Improving the treatment of patients.
- Optimization of new drug production [44].
- Improve the recognition of diseases.

- Reduce clinical trial time cost and failure rate of pharmacological clinical trials.
- Do away with the inefficient system of trial and error that swells the medical expenses and compromise the services of the patients [45].
- Personalized Therapies: Personalized medicine enables medical practitioners to prescribe specific therapies to the target patients, depending on their genetic composition, life style, and disease peculiarities. Such individualization enhances the possibility of a successful treatment and reduces the negative effects [46,47].
- Improve outcome: The improved clinical outcomes of personalized medicine can be achieved through the targeting of treatments to the molecular processes which drive the disease in the patient. This may comprise; improved disease management, lesser rates of recurrence, and improved survival rates [48].
- Optimized drug selection: Genetic testing and molecular profiling can be employed to determine a list of the most likely effective drugs in a particular patient and avoid trial and error applications and adverse drug reactions [49].
- Prevention and early detection: Personalized medicine lays stress on preventive healthcare that focuses on pro-active healthcare activities such as screening of potential risks of some diseases and the early diagnosis of illnesses on the basis of individual risks[50].This can help ease early interventions and preventive steps to ensure that the disease does not advance.
- Healthcare cost saving: Despite its possible initially higher costs in the form of genetic testing and diagnostics, personalized medicine can result in cost reductions in health care by decreasing hospitalizations and complications[51].This is opportunities of value based collaboration with healthcare payment and care delivery organizations.
- Reduced Development Costs: Personalized medicine can be used to reduce drug development costs by defining the patient subpopulations most likely to respond to a drug in the clinical trials and minimize the overall costs of drug development. This is a specific process that enhances chances of success in clinical trials and lowers chances of late-stage trials failure[52].

- Longer Patent Life: Drugs that have been generated using personalized medicine systems can be potentially subjected to longer patent periods in the event that they can target a specific genetic mutation or biomarker [53]. Such exclusivity may give pharmaceutical organizations further time to recover investments in research and development and profit.
- Personalized medicine Empowers patients: Personalized medicine empowers patients in the fact that it involves them in making their own decisions regarding their healthcare. The patients can make a decision that would fit their values and preferences through learning their genetic risks and therapies [54].
- Research and drug development: Medicine personalization will generate gigantic information on hereditary variability, illness pathology and pharmaceutical reactions that will be accessible in future research and drug development programs [55].It will result in creation of more precise treatment, and study additional about complex illnesses.
- Competitors: The companies that have been ahead in developing the personalized medicine strategies have an opportunity of being leaders in the industry with the healthcare providers and patients. This competitive border for transferred to the long term profitability and market dominance [56].
- Personalized medicine can improve drug selection and precision therapy, reduce adverse reactions, improve patient compliance, transform medicine into a preventative rather than a responsive strategy, improve cost-efficiency, and increase patient confidence in the use of innovative treatment methods and redefine the role of medicine in the healthcare system [57].

The role of the pharmacist

Pharmacists are important in personalized medicine as they help in the connection between medical care givers, patients and the individualized treatment programs. This is the contribution of pharmacists:

- **Medication Management:** Pharmacists are professionals in medication management. In personalized medicine, they allow assuring that the kind of medication assigned to an individual patient is focused on his or her genetic makeup, medical history, and other important points. They are able to manipulate dosage, choose proper formulations and medication responses [58].

- **Genetic Counseling:** Genetic counseling to patients undergoing genetic testing is also a service that can be offered by pharmacists as part of personalized medicine. They help the patients to specify the medical implication of the medical test results including the potential drug interaction, risk, and advantages [59].
- **Genetic data interpretation**: Pharmacists are better positioned to interpret genetic data and use them to make medication choices and dosages.
- **Adverse drug Reaction Management:** Pharmacists get educational training on how to identify and deal with adverse drug reaction. They are very important in personalized medicine to determine and counter antimedical reactions that can occur as a result of genetic diversity or other personal causes [60].
- **Patient Education and Counseling:** Pharmacists also provide education and counseling to patients with regards to their medications, mode of action, side effects, and the need to adhere to them [61]. They also offer specialized education in personalized medicine where they assist patients in knowing the ways in which their genetic makeup affects the way they respond to treatment.
- **Cooperation with Healthcare Team:** Pharmacists also cooperate with other healthcare providers such as physicians, genetic counselors, and other professionals in order to come up with complex individualized treatment plans to patients [62]. They use their skills in drugs administration in order to make sure that the treatment is safe, effective, and properly combined with other patient care elements.
- **Research and development:** Pharmacists can also take part in research and development work connected to personalized medicine, such as development of pharmacogenomic examinations, novel medication treatments and novel medication management techniques [63].

With the growing adoption of personalized medicine into the clinical environment, it is essential that the pharmacists are aware of developments in its possible uses in diagnosing, treating, and preventing particular diseases, along with recent approvals and research. According to literature, pharmacists who can capitalize on their pharmacokinetics and pharmacodynamic knowledge can have significant role to play in increasing awareness about pharmacogenomics and personalized medicine [64]. As an example, the American Society of Health-

System Pharmacists (ASHP) recommends that pharmacogenomic testing is likely to improve medication related outcomes in different healthcare environments. ASHP states that the benefits may include a reduction in poor clinical outcomes, reduced cost of treatment, enhanced level of medication compliance, enhanced choice of treatment agents, reduction in the length of treatment, and more safety of the patient because of the participation of a pharmacist. Moreover, as a result of their competence, pharmacists can be an important part of the work on cooperation with clinicians to guarantee optimal choice and dosage of medicine in accordance with the findings of pharmacogenomic tests [65]. Overall, in personalized medicine, pharmacists play an eminent and multidimensional role, with the possibility of applying their medication management, genetic, and patient care knowledge to improve the effectiveness of the treatment provided to a specific patient.

Personalized medicine may seem to many people as the sole-purpose name that concentrates on individualized care. Nonetheless, the Wikipedia definition includes a focus on patient specific approaches whereas the Presidential Council specifically states subpopulations as opposed to individual patients. On the contrary, the definition proposed by the National Cancer Institute does not specify whether personalized medicine addresses individuals or subpopulations. The examination of the most common illustrations of personalized medicine, including the application of HER2-trastuzumab, we learn that a small sub-population of women with early breast cancer has tumors expressing HER2, and thus, can be treated with the trastuzumab, which is effective against this type of tumor. However, as the entire group of this subgroup is all treated with trastuzumab the same way (e.g. same dosage schedule), it is often viewed by many example of subgroup or stratified medicine [66].

Emerging trend findings in personalized medicine

Table No 2. Emerging trend findings in personalized medicine

Sr.No	Trend	Key Finding	Examples
1	Pharmacogenomics Genetic Tailoring of Anesthetics.	Genetic differences play an important role in determining anesthetic drug metabolism, efficacy, side effects, and risk of complication to allow an individual choice of drug and dosage.	Recruitment of CYP450 polymorphisms which influence the metabolism of anesthetic agents; OPRM1 μ-opioid receptor polymorphs which alter the response of opioids[67].
2	AI-Enhanced Preoperative Decision Support.	Notable result AI models enhance the process of risk stratification, clinical decision-making, and safety associated with patient multidimensional (genomic, clinical, physiological) data analysis.	Predictive analytics minimizing hypotension and assisting anesthesia titration via closed-loop controls; predicting risky preoperative events[68].
3.	Multi-Omics & AI Biomarker Discovery Enables Precision Diagnosis	Integrating genomics, proteomics, and epigenomics with AI enhances identification of biomarkers for psychiatric disorders, paving the way for personalized treatment pathways.	Precision psychiatry review explains how multi-omics data interpreted through AI can reveal complex biological signals underlying mental health disorders[69].

4	AI Enhances Diagnostic Accuracy	AI models (ML/DL) outperform traditional methods in diagnosing psychiatric disorders by leveraging diverse data sources like EEG, imaging, and behavioral metrics.	Meta-analysis reports AI diagnostic accuracy ~85%, showing utility in real-world clinical settings[70].

Future of personalize medicine.

The concept of personalized medicine is currently being discussed as a fundamental element of the new era in healthcare [71].It is the shift of the paradigm of medical treatment and intervention to the personal attributes of each patient. It is a method that recognizes the genetic difference, lifestyle and environmental factors that make a person vulnerable to health and illnesses.

Many experts, scientists, and practitioners have emphasized the disruptive potential of personalized medicine in enhancing patient outcomes, preventing care and optimizing therapeutic regimens [72].The continued growth of technology, especially in the areas of genomics, proteomics, and data analytics of personalized medicine into the mainstream healthcare practice. The issue of ethical considerations, and regulatory frameworks are involved, the general trend would indicate that personalized medicine will become an even more dominant factor that will influence the future of healthcare [73].

CONCLUSION

Personalized medicine represents a huge transformation in the health care system since it offers customized treatment to the individuals considering the genetic, lifestyle and disease determinants of an individual. It is a bright idea on how to benefit the patient, minimize the side effects, and revolutionize medical care. It is more effective because it will also guarantee prevention and proactive in healthcare by personalizing therapies according to patient groups and genetic indications. Personalized medicine infiltrates the field of innovation in designing drugs, diagnostics and health provision thus leading to a higher and more efficient medical intervention. Even though implementation will be faced by initial

challenges and costs. The overall returns of personalized medicine are enormous since they are associated with the increased patient satisfaction, and overall improved medical research. Personalized medicine. In the future will your entire genetic code be available at birth, stored in personalized medical records. This knowledge would help the physicians and clinicians develop more effective healthcare intervention relying on the predispositions of individuals to various disease

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Chapter 3: Chalcone Scaffolds as Bioprecursors of Flavonoids: Chemistry, Pharmacokinetics, and Therapeutic Potential

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Abstract:

The chalcone structure, a precursor (open chain) of the flavonoid family has become a privileged structure in medicinal chemistry due to its synthetic flexibility and wide pharmacological potential. In this review, the chemical structure of chalcones and their biosynthesis pathway (chalcone synthase) as well as the important synthetic strategies are critically examined. It then outlines the key pharmacokinetic issues, including the largest first-pass metabolism, which limits oral bioavailability, and outlines structure-property relations that are used in optimisation. The therapeutic panorama is comprehensively covered, and it includes anticancer, anti-inflammatory, neuroprotective, antimicrobial, and metabolic actions with a focus on the key processes like the regulation of NF-kB, Nrf2, and tubulin dynamics. The importance of ring substitution and the indispensable a,b -unsaturated ketone linker has been resolved using structure-activity relationship (SAR) analysis. Despite the exceptional preclinical activity of a number of rationally designed derivatives and the patents on several advanced formulations, there is a strong sense of clinical translation gap outlining a large translational gap. The future factors will be based on the acceptance of chalcones as rational multi-target directed ligands (MTDLs), applying systems biology to elucidate the mechanism holistically, and use advanced nanotechnology to deliver the drugs more effectively. The synthesis of chalcone scaffold shows how a simple plant metabolite has been used as a platform in the development of new therapeutic agents against complex diseases.

Keywords: Chalcone scaffold, Flavonoid bioprecursors, Pharmacokinetics, Structure-activity Relation (SAR), Therapeutic potential, Multi-target directed Ligands (MTDLs), Targeted drug delivery, Natural products, Drug discovery.

Introduction:

The tireless hunt of new pharmacophores in the enormous array of chemicals found in nature has continued to produce frameworks of enormous therapeutic worth. The flavonoid family is one of them, and decades of research have proven its versatility in relation to human health and disease control [1]. But there has been a paradigm shift whereby more and more focus has been on the metabolic precursors of these ubiquitous compounds the chalcones. The open-chain flavonoids, often overshadowed by their more structurally complex cyclic counterparts are now also being considered as not just being transient biosynthetic intermediates but also having their own bioactivity. Their remarkable pharmacological versatility is not characteristic of their inherent chemical simplicity thus rendering the chalcone scaffold a privileged structural motif in contemporary biomedical chemistry and drug discovery in contemporary times [2].

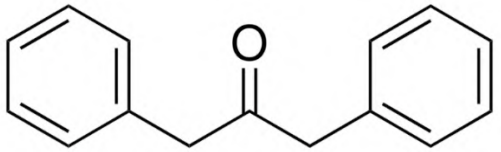
1.1. Historical Context and Natural Occurrence of Chalcones

The history of chalcones is closely connected with the one of traditional medicine. Plants high in these compounds have been used in an array of cultures long before their chemical isolation due to their alleged anti-inflammatory, antimicrobial and their alleged detoxing ability [3]. An example is that the genus Glycyrrhiza (licorice) and Angelica were commonly used in Eastern pharmacopoeias, and modern day analysis has established the chalcones as major components that underlie several of their observed effects [4]. The very word chalcone, a Greek word chalcos, meaning bronze, is a reference to the yellow-orange coloration many of these compounds give to flowers, fruits, and woods, which has essential ecological functions in the UV protection system and pollination. They are very abundant in natural state, but unevenly distributed; being most abundant in the families Fabaceae, Asteraceae, and Moraceae. Two of the most studied natural chalcones are isoliquiritigenin of licorice and xanthohumol of hops (Humulus lupulus) which are used as examples in the study of the scaffold bioactivity [5].

1.2. Defining Chalcones: The Open-Chain Flavonoid Precursors

Chalcones can be characterized chemically as a simple but elegant structure: 1, 3-diphenyl 2 -propen 1 -one. This is a two-aromatic ring structure (Ring A and Ring B) connected through a highly reactive a,b -unsaturated ketone bridge - an enone system.

The enone moiety is the pharmacophoric heart of the chalcone framework, which gives the molecule electrophilic properties allowing it to form reactions with biological nucleophiles like cysteine residues in essential cellular proteins with ease [6]]. This is the opposite of most flavonoids, which have closed, heterocyclic C -rings (such as the chroman in flavanones or the pyrans in flavones and flavonols). This ring closure is lacking making chalcones conformationally flexible and metabolically prepared to undergo transformation. It is in this loosely-linked nature that makes them the natural bioprecursors to which the complete flavonoid repertoire is enzymatically built.



1,3-Diphenyl-2-propanone

1.3. The Central Role in Flavonoid Biosynthesis: An Overview

The production of flavonoids exemplifies an exemplary story of plant secondary metabolism and chalcones are unquestionably placed at the initial committed step. A type III polyketide synthase, the enzyme chalcone synthase (CHS) catalyses the serial condensation of a single molecule of 4 -coumaroyl -CoA with three molecules of malonyl -CoA. This beautiful series of reactions gives naringenin chalcone the typical starting material of flavonoids [7]. This is then followed by the ring-closing reaction that is catalyzed by the chalcone isomerase (CHI) that stereospecifically cycles the chalcone into (2S) -flavanone. It is a pivotal biosynthetic crossroad; based on the flavanone backbone, oxidative derivations, hydroxylations and glycosylations differ to produce the incredible variety of over 9000 known flavonoid structures, comprising flavones, flavonols, anthocyanins, and isoflavonoids. The central metabolic role of the chalcone in this pathway is emphasized, but the idea of a more metabolically significant relationship between the biological actions of most flavonoids and their potential metabolic interconversion to or via chalcone-like intermediates in vivo is also suggested by this pathway. [8]

The aim of the present review is to summarise the modern research to provide a unified and critical evaluation of chalcones as an extension of their classical use in biosynthesis as intermediates. The main idea behind our work is to transform the chalcone skeleton into a dynamic pharmacophore with its specific benefits and limitations. It has a very complex biosynthesis and a very complex chemistry; we will first break down its basic chemistry and the intricacies of its biosynthesis. The basis of our discussion will then examine in detail the pharmacokinetic profile of chalcones, a subject that is often ignored, but must be used to determine how the potency in vitro can be translated into

the efficacy in vivo. We will comprehensively assess their therapeutic potential with regard to oncology, metabolic disease, neurology, and infectious disease, and the major emphasis on structure-activity relationships which are rationally deployable. Notably, high-impact studies published within the past decade will be included in the current review, inconsistencies in the literature will be determined, and the controversies on the main molecular targets of specific chalcones will be indicated as well as gaps in the literature. The following chapter attempts to develop chemical intuition, concepts of biological process and translational drug development in an effort to elucidate the entire potential of the chalcone scaffold as an inert source of new, multi-target therapeutic agent.

Table 1: Representative Natural Chalcones, Their Sources, and Core Biological Activities

Chalcone Compound	Primary Natural Source	Notable Reported Pharmacological Activities
Isoliquiritigenin	*Glycyrrhiza glabra* (Licorice)	Chemopreventive, anti-inflammatory, cardioprotective [5, 9]
Xanthohumol	*Humulus lupulus* (Hops)	Anticancer, antioxidant, anti-angiogenic [5, 10]
Butein	*Rhus verniciflua* (Chinese lacquer tree)	Anti-inflammatory, AMPK activator, anti-diabetic [11]
Phloretin	Apple tree (*Malus domestica*) bark/leaves	Antioxidant, glucose transporter (GLUT) inhibitor [12]
Cardamonin	*Alpinia katsumadai*, *Boesenbergia rotunda*	Anti-cancer, NF-κB inhibitor, Nrf2 activator [13]

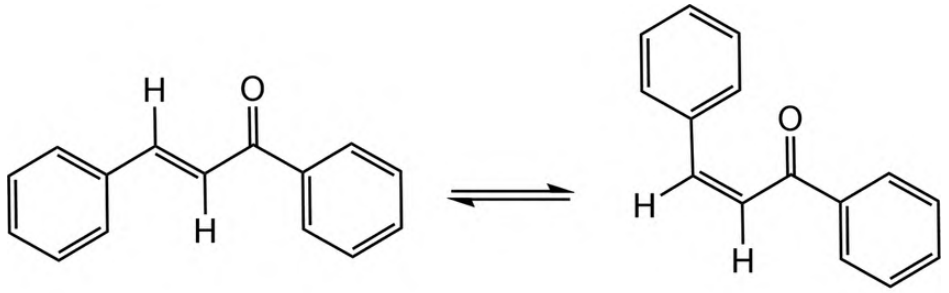
2. Chemistry and Biosynthesis of Chalcones

The medical potential of any scaffold of natural products is inherently based upon an accurate explanation of its chemical structure and the way it is acquired in living cells. In the case of chalcones, this knowledge discloses a molecule of apparent simplicity, with whose chemical reactivity and biosynthetic rationale is the biological usability directly dependent. The paper breaks down the fundamentals of chalcone chemistry, including the structure of atoms, the synthesis in industry, and the beautiful example of an enzyme-based pathway that has placed them in the centre of flavonoid variety in the plant kingdom.

2.1. Chemical Structure and Nomenclature

2.1.1. Core Scaffold and Isomerism

The backbone of the chalcones is the 1, 3 -diphenyl -2 -propen -1 -one system (IUPAC). This comprises two benzene rings (named the A-ring (due to the acetate/malonate pathway) and the B-ring (due to the phenylpropanoid pathway)) linked by a three-carbon a,b -unsaturated enone linker (-CO -CH =). This bridge is not such a static bridge but a center of chemical reactivity. The geometry of the conjugated π -system planar to the carbonyl and the vinyl double bond is important, and it is what allows electron delocalisation. This conjugation explains the typical UV- Vis absorption (maximum wavelength usually between 300-400nm) and pigmentation reported in the literature



[14]. E-isomer Z-isomer

An important characteristic that this structure gives rise to is isomerism. The fact that the chain lacks rotation around the double bond of the propenone chain will result in cis (Z) and trans (E) isomers. The trans (E) isomer in almost every biologically relevant case is much more stable and dominant because there is less steric clash of the A -ring with the carbonyl oxygen. The cis (Z) form may occur under certain conditions or by photoisomerisation, which makes the phenomenon able to induce considerable changes in the biological activity and deserving attention in stability investigations of pharmaceutical preparations [15].

2.1.2. Substitution Patterns and Derivatives

The backbone of the chalcones is the 1, 3 -diphenyl -2 -propen -1 -one system (IUPAC). This comprises two benzene rings (named the A-ring (due to the acetate/malonate pathway) and the B-ring (due to the phenylpropanoid pathway)) linked by a three-carbon a,b -unsaturated enone linker (-CO -CH =). This bridge is not such a static bridge but a center of chemical reactivity. The geometry of the conjugated π -system planar to the carbonyl and the vinyl double bond is important, and it is what allows electron delocalisation. This conjugation explains the typical UV- Vis absorption (maximum wavelength usually between 300-400nm) and pigmentation reported in the literature [14].

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Ring A Substitutions: The commoner hydroxylation at 2′ and / or 6' is less common in natural chalcones although undertaken synthetically. Hydroxylation or methoxylation is common at 4 -position.

Ring B Substitutions: This ring exhibits tremendous variability. Patterns such as 4-hydroxy, 3,4-dihydroxy (catechol), 2,4-dihydroxy, or 4-hydroxy-3-methoxy are prevalent in nature. Prenylation or other alkylations on the B-ring, as seen in xanthohumol, dramatically increase lipophilicity and can alter target specificity [17].

The term "chalcone" itself often refers to the simplest unsubstituted parent compound. Specific derivatives are named as substitution patterns on this parent system (e.g., 2',4'-dihydroxychalcone) or by common names derived from their plant source (e.g., isoliquiritigenin for 2',4',4-trihydroxychalcone). Hybrid derivatives, where one ring is replaced by a heterocycle (e.g., pyridine, furan), are a major focus of contemporary medicinal chemistry to fine-tune properties.

2.2. Biosynthesis in Plants: The Chalcone Synthase (CHS) Pathway

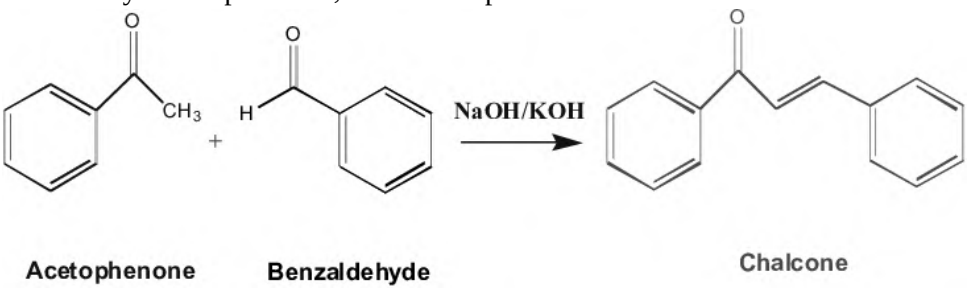
Chalcone production in plants is catalysed by an enzyme, chalcone synthase (CHS). CHS is the penumbral form of type III polyketide synthase and is involved in the pivotal point where primary metabolism is split to flavonoid production. It reacts through a stepwise decarboxylative condensation. CHS initially binds an initial molecule, usually 4 coumaroyl -CoA (the product of phenylalanine through the phenylpropanoid pathway) into its active site. It subsequently catalyses the addition of three molecules of malonyl-CoA to it, each addition being preceded by decarboxylation, to produce a tetraketide intermediate [18]. This linear precursor is subjected to an intramolecular Claisen-type cyclisation and aromatisation and always forms the A-ring, to give naringenin chalcone (4,2A42C6X)-tetrahydroxychalcone. The specific steric and electrostatic derivations of the active -cavity that determinesthis stereospecific folding have been described by recent structural biology research, such as X-ray crystallography of CHS complexes with substrate analogues, and so explain the high regioselectivity of nature [19].

2.3. Key Chemical Reactions and Synthetic Methodologies

2.3.1. Claisen-Schmidt Condensation

The ClaisenSchmidt condensation, the base catalysed cross-aldol reaction of an acetophenone (to the A-ring) and a benzaldehyde (to the B-ring) has remained the cornerstone of the synthesis of chalcones. This reaction is normally performed using

hydroxides or alkoxides in alcoholic solvents and occurs either through the formation of enolates by reacting the ketone with hydroxides, followed by nucleophilic attack of the aldehyde carbonyl, and then as due to the loss of water to give the a,b -unsaturated system [20]. Although strong, classical conditions may be affected by side reactions, including poly-condensation or aldol addition reversibility especially with electron-deficient substrates. Base strength, solvent polarity and temperature are therefore a recurring theme in synthetic protocols, which are optimized.



2.3.2. Novel Synthetic Approaches and Green Chemistry Methods

Under the pressure of efficiency, selectivity, and environmental sustainability, there has been a great methodological development. These include:

Solid-supported catalysis: heterogeneous catalysts like hydroxyapatite-supported alkali metals, amine-functionalised silica gels, etc., are used which allow easy product recovery and reuse of the catalysts [21].

Solvent-Free and Mechanochemical Synthesis: By using grinding (ball milling) of solid acetophenone and benzaldehyde derivatives with a basic catalyst like K_2CO_3 or NaOH, both wastes are minimized and yields are increased by avoiding use of volatile organic solvents [22].

Organocatalysis and Microwave Assistance: Organocatalysts using Proline: In some asymmetric reactions, very high levels of stereocontrol may be achieved using organocatalysts based on proline. Reaction times can be reduced dramatically, going down to minutes, microwave irradiation increases energy efficiency and often gives more clean product profiles [23].

Such green chemistry discoveries do not constitute merely academic practices but are progressively becoming essential in the upscale and sustainable syntheses of chalcone libraries with an aim of high-throughput screening.

2.4. Cyclization to Flavonoids: Mechanisms and Products

2.4.1. Formation of Flavanones (The First Cyclization Step)

The conversion of a linear chalcone to a cyclic flavanone occurs with amazing efficiency and stereospecificity in plants, which is catalysed by chalcone isomerase (CHI). CHI catalyses a 6-endo-trg cyclisation whereby the nucleophilic 2- position phenolic oxygen

on the nucleophilic site 2- attacks the electrophilic 1, 2-unsaturated system at the 3-carbon. This forms a new stereogenic centre at C 2, where CHI exclusively forms the (2S) -flavanole analogue, as in naringenin [24]. The rate acceleration by the enzyme is remarkable, and the reaction is much faster, billions of times faster, than the non-stereoselective unrestricted cyclisation. At mild acidic or basic pH, chalcones can cyclise non-enzymatically in vitro however, this reaction normally provides racemic mixtures of flavanones, highlighting the level of control that CHI has in vivo.

2.4.2. Diversification into Other Flavonoid Classes

The product of the (2S)-flavanone reaction is the direct substrate of a group of modifying enzymes which jointly promote flavonoid differentiation. Flavanone 3 -hydroxylase (F3H) adds an additional hydroxyl group at C -3, producing dihydroflavonols. This is further oxidized by the flavonol synthase (FLS) to produce flavonols (e.g., quercetin). In other cases, it is possible that flavones (e.g., apigenin) can be produced by isomerization catalyzed by chalcone isomerase-like proteins or specific synthases [25]. The CHS/CHI couple is initiation of this enzymatic cascade which is tightly regulated and tissue selective hence explaining the unique flavonoid profiles being apparent in different plant organs. Pharmacologically, the given interconnectivity of biosynthesis suggests that, in vivo, the administered flavonoids can be converted through the metabolism into the chalcone-like concatenates, making it difficult to pinpoint the biological activity to a single molecular substance.

Table 2: Comparison of Classical vs. Green Methodologies for Chalcone Synthesis

Parameter	Classical Claisen-Schmidt (Solution-Phase)	Green Methodologies (e.g., Solvent-Free Grinding)
Typical Conditions	NaOH/EtOH, reflux, 2-12 hours	K_2CO_3, ball mill, room temperature, 30-60 min
Solvent Use	High (ethanol, methanol)	Negligible to none
Energy Input	High (heating under reflux)	Low (mechanical energy)
Work-up & Purification	Often requires aqueous wash, extraction, chromatography	Frequently simple washing or recrystallization
Catalyst Recovery	Difficult, usually homogeneous	Easier with solid-supported catalysts
Environmental Impact (E-factor)	High	Significantly Lower
Typical Yield Range	Moderate to High (50-90%)	Often Very High (80-95%)
E-factor: kg waste / kg product, a key green chemistry metric. Adapted from principles in [21, 22].		

3. Pharmacokinetic Profile of Chalcones

The high in vitro bioactivity of chalcones that has a range of micromolar to sub-nanomolar potency against most drug targets inevitably faces the daunting obstacles of in vivo pharmacokinetics. In the scheme regulated by absorption, distribution, metabolism, and excretion (ADME), numerous leads based on natural products fail. The pharmacokinetic phenotype of chalcones is therefore defined as having foreseeable barriers due to their polyphenolic structure, and peculiarities due to the reactive enone core. Such a profile requires a thorough assessment to be done in rational drug design, to inform structural changes that would improve the systemic exposure and therapeutic activity of the drug.

3.1. Absorption and Bioavailability

Oral bioavailability is the major pharmacokinetic bottleneck in most chalcones. Their uptake is a disputed interaction between passive diffusion and active transport which is highly regulated by solubility and intestinal metabolism. Chalcones, as a class, are often poorly soluble in aqueous solution, because the aromatic rings of the molecules are lipophilic and thus do not readily dissolve in gastrointestinal fluids, a very crucial first step to absorption [26]. However, the intrinsic permeability tends to be good, as witnessed in the Caco 2 monolayer experiments with the use of compounds like isoliquiritigenin, which proposes the view that such compounds are not actively effluxed by P -glycoprotein [27].

It is the concept of bioavailability that deserves a careful dissection. Absolute oral bioavailability of parent chalcones is rarely greater than 10‥ in rodents, but this amount is frequently a result of an extensive first-pass metabolism, but not intrinsic absorption shortcomings. As an example, xanthohumol literature demonstrates that, although the parent molecule is barely observed in plasma, its phase 2 metabolites (glucuronides and sulfates) reach high levels in the body, suggesting that absorption takes place and phosphorylation occurs after entering the enterocytes and hepatic tissue [28]. Therefore, to provide a comprehensive profile, pharmacokinetic analyses should be both on the parent drug and its principal metabolites.

3.2. Distribution and Plasma Protein Binding

Chalcones and their metabolites show moderate or wide tissue distribution once they are introduced into the systemic circulation, but volume of distribution (V -1d) is rarely very large. Its distribution is limited by a strong affinity between the drug and human serum albumin (HSA). The binding affinities can be fairly strong; the binding of chalcones like hesperidin methyl chalcone to the binding site (Sudlow, 1967) of HSA has binding

constants (K b) of the order 10 4 M 1. This elevated binding (>90 many derivatives) produces a large reservoir of compound and at the same time decreases the number of free, pharmacologically active molecules that can go through the cell membranes and interact with therapeutic targets. It has been distributed to particular organs, such as the liver (the main location of metabolism) and tissues with inflammation or neoplasia (vascular permeability might be increased), which should be confirmed by quantitative imaging.

3.3. Metabolism (Biotransformation)

The most significant driving power in controlling the pharmacokinetic properties of chalcones is metabolism, which is a two-sided sword: it causes a rapid clearance but may generate active metabolites.

3.3.1. Hepatic Metabolism: Phase I and Phase II Reactions

The aromatic ring stability of the chalcone skeleton limits phase 1 transformations of the parent skeleton. The most vulnerable locus is the enone bridge that can be reduced by the carbonyl reductases or aldo-, keto-reductases to form dihydrochalcones-a reaction that generally destroys the requisite of the Michael acceptor to be biologically reactive [30].

Phase II conjugation is actually the major route of metabolism. Chalcones are highly productive substrates of uridine 5 0-diphospho-glucuronosyltransferases (UGTs) and sulfotransferase (SULTs) and glucuronide and sulfate conjugates rapidly and extensively form in the phenolic hydroxyl positions. This conjugation takes place pre-systemically in the intestinal mucosa, and systemically in the hepatic tissue. Licochalcone A was observed to be glucuronidated instantly in a rat model; in minutes of administration, the glucuronidated metabolite was observed in a higher concentration than conjugate in circulation; the AUC of the conjugate was over twenty times that of the parent molecule [31]. Even though these polar conjugates are typically considered inactive with regard to the original target (e.g., NF -¿B inhibition), they can still have specific biological activity, or can be hydrolyzed back to the aglycone in target tissues by enzymes like 2 -glucuronidase, which is commonly upregulated in an inflammatory or tumorous microenvironment..

3.3.2. Role of Gut Microbiota

Gastrointestinal microbiome is a critical, changeable extra-hepatic metabolic compartment. The commensal bacteria have a range of enzymes-like 2-glucosidases, glucuronidases and reductases which are capable of remodeling chalcones significantly. They can also deconjugate metabolites excreted in the bile to the aglycone, which leads to enterohepatic recirculation and may prolong residence time, but on the cost of the pharmacokinetic modeling [32]. In addition, ring fission of the chalcone B -ring via microbiota can form smaller phenolic acids (e.g. phloretic acid of phloretin), which have systemic effects, but form part of a terminal metabolic pathway of the parent scaffold.

Inter-individual differences in microbial composition can therefore be considered an important, yet frequently neglected, factor of pharmacokinetic variation of orally delivered chalcones.

3.4. Excretion

The excretion of chalcones is mainly excreted through the kidney and bile. The filtration and active secretion is effective in excretion of highly polar glucuronide and sulfate conjugates to the urine. The conjugates of more high molecular weight, especially diglucuronides, are more likely to be excreted to bile by transporters like MRP2 (ABCC2) [33]. The magnitude of the biliary excretion is capable of inducing enterohepatic recirculation as demonstrated by secondary peaks in plasma concentration-time profiles..

The half-life (t1/2) of most chalcone aglycones is short, often ranging from 1 to 4 hours in preclinical models, reflecting rapid conjugation and clearance. However, the t1/2 of total metabolites (conjugates) may be longer.

3.5. Structure-Pharmacokinetic Relationship (SPR) Insights

The new SPR research gives principles on how the chalcone pharmacokinetics can be enhanced:

Hydroxylation vs. Methoxylation: Multiple free phenolic -OH groups although advantageous to antioxidant activity and target binding, form the major loci at which the target is rapidly conjugated. Phase II metabolism is inhibited by methoxylation (–OCH 3) at these sites and consequently, the phase II metabolism is significantly diminished improving metabolic stability and plasma half-life. An example is a methoxylated derivative of isoliquiritigenin that increased the half-life of rats by five times when compared to its hydroxylated analogue [34].

Lipophilicity and Absorption: Increasing lipophilicity (e.g., through prenylation, e.g. with xanthohumol) usually increases membrane permeability but can also reduce aqueous solubility and increase affinity to enzymes, e.g. CYP450s.

The enone Bridge Reduction: Reductions in the double bond of the enone bridge (to make dihydrochalcones) not only alter pharmacodynamics, but also abolish a possible phase I reduction site, giving it a significant enhancement in metabolic stability.

3.6. Challenges and Strategies for Bioavailability Enhancement

The key difficulty is to balance the critical pharmacophoric characteristics (the enone, particular hydroxyl groups) with the metabolic vulnerabilities to which they lead. Blocking all metabolic sites would only pose the risk of making the compound inert. In turn, modern approaches focus on formulation and prodrug:

Nanotechnology-Based Delivery Systems: The efficacy of lipid-based nano carrier, including self-nanoemulsifying drug delivery system (SNEDDS), has been established. Oral bioavailability of a SNEDDS formulation of bergenin (a C-glycosidic

dihydrochalcone) in rats was increased by more than 300 % by increasing the dissolution and lymphatic transport of bergenin, thus avoiding first-pass metabolism [35].

Complexation with Cyclodextrins: Aqueous solubility may be increased by example of inclusion complexes with β -cyclodextrin or its derivatives, which also physically protects the reactive enone moiety form degradation and metabolism by enzymes in the gastrointestinal tract [36].

Phospholipid Complexation (Phytosomes): Interaction of chalcones like silybin (a flavonolignan with dihydrochalcone subunit) with phospholipids produces complexes which enhance the absorption by facilitating the insertion into phospholipid bi-layers of enterocytes [37].

Specific Prodrug Design: Prodrug design in which phenolic -OHs are esterified with promoieties (present in disease-targeting locations) that are cleaved by disease-specific enzymes (e.g. by the tumour tissue-estersterase) selectively is a way to protect the target compound against systemic conjugation and achieve targeted activation [38].

Concisely, the pharmacokinetic profile of a chalcone is characterized by an admirable absorption in opposing with the omnipresent and rapid phase II metabolism. The state-of-the-art goes beyond recording this weakness of Achilles to actively using SPR knowledge and advanced drug delivery technologies to design solutions. However, there is still a significant lack of knowledge about the in vivo role of microbiota -derived metabolites and the clinical translation of new delivery systems between preclinical proof-of-concept and scalable robust formulations. This artificial pharmacokinetic optimization forms the key to the achievement of the therapeutic potential which follows in the following section.

4. Therapeutic Potential and Pharmacological Activities

The development of chalcones as simple biosynthetic intermediates to highly desirable therapeutic candidates is based on the proven ability to interact with a wide range of biological targets and pathways. Their inherent chemical reactivity, which is the α, 8 unsaturated ketone system, enables the interaction with key cellular proteins both covalently and non-covalently, and consequently, provides a polypharmacological profile that becomes more and more appealing to the treatment of multifactorial and complex illness. This part is a critical analysis of the evidence of these activities, going beyond an enumeration of the effects and decomposing underlying processes, comparing the strength of various major derivatives, and considering situation-specific issues and inconsistencies in the literature.

4.1. Mechanisms of Action and Key Molecular Targets

The major mechanistic theme that has been built upon chalcone pharmacology is that they are Michael acceptors. The nucleophilic attack of cysteine thiol groups on the electrophilic 2 -carbon of the enone system leads to the covalent modification of the

system. This supports anti-enzyme and anti-transcription factor activating against enzymes and transcription factors with important cysteine residues, including Keap1 (regulator of Nrf2), I k B kinase (IKK), and elements of the STAT3 pathway [39]. Covalent mechanism has the power to produce powerful and sustained inhibition but it also poses selectivity issues thus off-target effects may arise.

In addition to covalent modification, the chalcones show considerable non-covalent target interaction. They have the ability to intercalate into DNA and prevent tubulin polymerization, by binding at the colchicine site and also as competitive inhibitors of enzymes like protein tyrosine phosphatase 1B (PTP1B), cyclooxygenase 2 (COX 2), and aromatase [40]. Their conjugated structure is also planar allowing interaction with ATP-binding pockets of kinases.

4.2. Anticancer and Chemopreventive Properties

An example of the most actively explored anticancer scaffolds of natural product derivatives is chalcones. They are seldom monomechanistic in their activity and are formed by a concerted attack on several characteristics of cancer.

4.2.1. Apoptosis Induction

A mass of literature has shown that chalcone induces apoptosis in various cancer cell lines. It is often mediated by the intrinsic (mitochondrial) pathway, which is a loss of mitochondrial membrane potential, cytochrome c release, and caspase -3/9 activation. In bladder cancer cells, Licochalcone A triggers apoptosis by increasing pro-apoptotic Bax, decreasing anti-apoptotic Bcl -2, and triggering ER stress [41]. One of the controversies in the literature concerns the role of reactive oxygen species (ROS); although some chalcones (e.g. containing catechol groups) are antioxidants, others, especially those with electron withdrawing substituents, may actually result in pro-apoptotic generation of ROS, indicating a structure-specific duality of action in redox modulation [42].

4.2.2. Cell Cycle Arrest

Chalcones are able to prevent cell cycle events, mostly at G2/M phase junction which is associated with their interference with the microtubule dynamics. Methylsulfonyl chalcone analogs have demonstrated the ability to inhibit the polymerization of tubulins with an equivalent potency as combretastatin A -4, resulting in a good G2/M arrest followed by apoptosis [43]. G1/S Arrest Arrest at G1/S phase has also been reported and is typically accompanied by downregulation of cyclin D1 and Cdk4/6 as seen with xanthohumol in hepatocellular carcinoma models [44].

4.2.3. Anti-angiogenic and Anti-metastatic Effects

In addition to cytotoxicity directly, chalcones inhibit tumour progression by attacking the tumour microenvironment. They prevent angiogenesis through the down-regulation of vascular endothelial growth factor (VEGF) and its receptor VEGFR-2.

Isoliquiritigenin inhibits neoangiogenesis of breast cancer models through inhibiting VEGF/VEGFR-2 signalling axis [45]. It prevents metastasis by activating inhibition of matrix metalloproteinases (MMPs, especially, MMP-2 and MMP-9) and inhibiting signs of epithelial-to-mesenchymal transition (EMT) including Snail and Vimentin.

4.3. Anti-Inflammatory and Immune-regulating Effects.

The anti-inflammatory activities of chalcones are one of the strongest effects of this type of chemical that were described in detail. First of all, chalcones suppress inflammatory signatures by blocking the NF -kB pathway which is a key mediator of inflammatory responses. Anti-inflammatory compounds like butein and cardamonin inhibit IKK activity, which, in turn, inhibits the destruction of IKB alpha and the following nuclear translocation of NF -. As a result, the expression of pro-inflammatory genes (COX 2, iNOS, TNF 2, IL 6) is suppressed [46, 47]. This mechanism of action locates chalcones above non-steroidal anti-inflammatory drugs (NSAIDs), in which COX inhibition mostly involves direct binding with the enzyme.

Also, chalcones regulate other key signaling cascades, such as those of the MAPK (p38, JNK, ERK) and JAK/STAT. A number of derivatives have exerted immunomodulatory effects by skewing macrophage polarization to an anti-inflammatory-reparative M2 phenotype rather than a pro-inflammatory M1 phenotype, and this has been of significant potential to chronic inflammatory diseases [48].

4.4. Neuroprotective and Antioxidant Effects.

It is a chemical structure that determines the antioxidant capacity of chalcones to a large extent. Derivatives containing many hydroxyl groups, especially in the ortho or para positions of the B -ring, display a strong free-radical scavenging activity and metal-binding ability. One of the pharmacologically relevant, though indirect, antioxidant pathways is the activation of the Nrf2/ARE pathway. Chalcones like 2 4-hydroxy-6-methoxychalcone alter cysteine residues on Keap1 that enhance Nrf2 nuclear translocation and the up-regulation of a set of cytoprotective enzymes (HO-1, NQO1, GCLC) [49].

The neuroprotective properties of chalcones in the development of disease models such as Alzheimer (reducing amyloid -aggregations, tau hyperphosphorylations), Parkinson (sparing dopaminergic neurons), and ischemic stroke are attributed to this dual antioxidant mechanism. A synthetic derivative was Chamextone-24, and it was shown to be effective in a murine model of cerebral ischemia-reperfusion injury, reduces the volume of infarct and enhances neurological outcome, which is attributed to concomitant Nrf2 activation and NF-kB inhibition [50].

4.5. Antimicrobial and Antiviral Activities Antiviral: These microorganisms exhibit antiviral activities as well Antimicrobial and Antiviral Activities Antiviral: Antiviral activities are also observed in these microorganisms.

Chalcones have a broad-spectrum antimicrobial activity that is mainly due to the disruption of microbial membranes and the inhibition of biomolecular syntheses of fatty acids by 8-hydroxy- 3- fatty acid synthesis essential enzymes such as 8-hydroxy- 3- fatty acid synthesis (FabH). Recent studies indicate that action against drug-resistant organisms has been taken; an example is chlorinated chalcone which has strong effects on methicillin-resistant Staphylococcus aureus (MRSA) by disrupting membrane integrity and disrupting biofilm formation [51].

Antiviral profile of chalcones has become a very important field. They may prevent the entry of the virus, its replication, and assembly. Some derivatives have shown promising action against SARS -CoV-2, by targeting the viral main protease (M 2pro) and papain-like protease (PL 2pro). Xanthohumol derivatives are low micromolar M^pro inhibitors in biochemical studies, highlighting their possible use as lead candidates in anti-coronaviral therapeutics [52].

4.6. Cardioprotective Benefits and Metabolic Benefits.

4.6.1. Anti diabetic Potential

Chalcones reduce hyperglycaemia in ways such as stimulating peripheral glucose uptake by activating AMPK and translocation of GLUT4, blocking of carbohydrate-digesting enzymes (α -glucosidase, α -amylase) and preservation of pancreatic 6 -cells. Isoliquiritigenin enhances the insulin sensitivity of diabetic rodent test subjects by stimulating the AMPK signal in muscle and liver [53]. There is an emergence of synthetic chalcones that have an insulin sensitization effect in addition to lipid-lowering effect, but with reduced adverse side effects of a full PPAR7 agonist like thiazolidinedione [54].

4.6.2. Antiobesity and Lipidlowering activity.

Adipogenesis inhibition Chalcones, including butein, suppress transcription factors, including PPAR 7 and C/EBP 7. They also facilitate lipolysis and fatty -oxidation. In models of high-fat diets, a number of chalcone derivatives lower the body weight gain, hepatic steatosis, serum triglyceride and LDL-cholesterol and increase the serum HDL-cholesterol [55].

4.7. Other New Therapeutic Areas.

New applications are constantly being discovered by continuing research. Some of the chalcones have been shown to have anti-fibrotic effects in hepatic and pulmonary models by blocking the TGF-1/Smad signaling. The others are promising in osteoporosis as they enhance differentiation of osteoblasts and inhibit osteoclastogenesis. Additionally, the

role of chalcones in regulating ferroptosis a regulated, iron-dependent cell death is also beginning to be explored: some of the analogs are ferroptosis inducers in cancer cells, others ferroptosis inhibitors in neurodegenerative settings, which is also revealing more aspects of their complex bioactivity [56].

5. Structure-Activity Relationship (SAR) Analysis.

The complexity of the relationship between the molecular structure and the biological activity of any pharmacophore ultimately limits the therapeutic potential of that specific pharmacophore. The SAR analysis of chalcones is not just a case of enumeration but it is also one of the most important blueprints of rational design of drugs. The elucidation of potency, selectivity, and the pharmacokinetic characteristics depends on systematic spatial variation of scaffold modifications to direct the exploration of chemical space around this framework core to drug candidates with desirable properties. It is a key factor in critically comparing both traditional and the modern SAR paradigms, finding areas of convergence and divergence, and manipulating the strategic scaffold to achieve therapeutic benefit.

5.1. Effects of Ring Substitutions (A and B Rings).

The aromatic rings provide the main modulators of target affinity and selectivity and the B-ring often has a stronger effect on the A-ring. These interactions are determined by electronic, steric and hydrogen bonds properties that have been added by the substituents.

One common pattern in several pharmacological endpoints is the structure-enhancing activities that electron-donating groups (EDGs) like hydroxyl (-OH) and methoxy (-OCH 3)confer to the B -ring. To achieve anticancer activity, a 4 7-hydroxyl or 3, 4 7-dihydroxyl (catechol) structure often relates to high-potency pro-apoptotic and anti-proliferative properties, which are explained by enhanced target protein interactions and redox cycling abilities. However, it is important to note that chalcones bearing 4 0 H group show better inhibition of tubulin polymerization compared to their analogues that are not substituted with 4 0 H group (59). On the other hand, electron-withdrawing groups (EWGs), such as halogen (-CL, -F) or nitro (-NO 2), tend to enhance anti-inflammatory and antimicrobial effects. The B-ring substitution with a 4 -chloro group has significantly enhanced the COX-2 inhibitory potential, and selectivity against COX-1, presumably by changing the electronic distribution and binding pocket interactions [60].

The substitution position is also vital. A 2 4 pattern on the A-ring is optimal in anti-diabetic chalcones against 4 -glucosidase, which produces a chelating site that interacts with the active site of the enzyme. In the case of inhibition of NF - -, a 2 -hydroxy group of the A-ring can form an intramolecular hydrogen bond with the carbonyl group of the

oxygen, keeping the molecule in a planar position that may increase intercalation or protein binding [61].

One of the most controversial aspects is the catechol moiety (3 4 O 2 H). Although it gives it strong antioxidant and Nrf2-activating functions, it is a significant site of rapid phase II metabolic conjugation (O -methylation, glucuronidation), resulting in poor pharmacokinetic properties. It can also be a cause of toxicity through redox cycling and quinone formation. This poses an inherent design conflict between making intrinsic activity as high as possible and maintaining metabolic stability.

5.2. Role of the α,β-Unsaturated Ketone Linker (Enone Bridge)

The enone bridge forms the non-negotiable pharmacophoric core which forms the basis of the typical biological reactivity of chalcones. Its structural integrity is vital in the mediation of activities via Michael addition. Weakening of the double bond to allow binding dihydrochalcones typically removes or significantly reduces activity on targets including IKK, Keap1, and tubulin, which confirms that α,β -unsaturation is required to bind covalently or with high affinity non-covalently [62].

However, the reactivity and selectivity can be fine-tuned by using minor changes of the linker. A massive substituent placed next to the ketone can sterically impede nucleophilic attack, which has the potential to decrease off-target covalent reaction and enhance the therapeutic index. The substitution of the ketone oxygen with a nitrogen, which produces an a,b-unsaturated imine or amidine, changes the distribution of electrons and hydrogen-binding ability- a strategy which has been pursued in the design of new protease inhibitors [63]. The geometry of the two bond is also an important factor; in general, the biologically active trans (E) isomer is many-fold more active than the cis (Z) counterpart because it has better conformational access to binding sites on its target.

5.3. Effects of Pre- and Post-Cyclization Modifications

The chalcone structure is present in a dynamic equilibrium with its cyclic flavonoid derivatives and alteration can be anticipated at various points along this biosynthetic chain.

Pre-cyclization changes include changes in the chalcone itself, including a large number of discussions. Post-cyclization alterations, however, look at the bioactivity of flavonoids and taking into account their possible metabolic transformation to chalcone-like intermediates. Indicatively, the activity of some flavanones depends on PH-dependent or enzyme-catalysed pH-dependent ring-opening to the chalcone counterpart in situ. This has given rise to the idea of such so-called masked chalcones, in which the cyclic form is a prodrug, which becomes more soluble or more stable until it reaches the target site (e.g., in an acidic tumour microenvironment) or is catalysed by certain enzymes to interchange into the active open-chain form [64].

The other approach is hybridisation, which is a combination of chalcone scaffold and other privileged pharmacophores. Chalcone-coumarin or chalcone-indole hybrids have

been developed resulting in compounds with dual mechanisms, including combined tubulin inhibition and topoisomerase poisoning, which can have synergistic activity as well as the ability to overcome drug resistance [65].

5.4. Designing Chalcone-Based Pro-drugs for Flavonoids

The inverse of the classical biosynthetic perspective in which chalcones are considered precursors of flavonoids is that certain flavonoids can be designed as prodrugs of chalcones. The reason is in the central pharmacokinetic drawback of chalcones that is a high metabolism and conjugation. It is possible to take advantage of ubiquitous human enzymes like β -glucuronidase or tumour-associated enzymes to release the active chalcone aglycone selectively in disease site by synthesising a flavonoid (e.g. a flavanone glycoside) which is enzymatically stable during absorption.

Recent efforts have been directed at enzyme-specific prodrug. As an example, a glucuronide prodrug of a cytotoxic chalcone is non-toxic in circulation, but is selectively hydrolyzed by high levels of 2 -glucuronidase in tumour necrotic areas, to produce high concentrations of the active agent in the local area and low levels in the rest of the system and toxicity [66]. On the same note, esters targeting phospholipase -A2 (overexpressed at sites of inflammation) or peptidase -activated prodrugs are in development. This mode of targeted activation is a highly developed SAR application, where chemical alterations are done not only to improve the endogenous binding, but to regulate rate, time, and place of release of active compounds intelligently.

Table 3: Key Structure-Activity Relationship Trends in Chalcone Pharmacology

Structural Feature	Target/Activity Enhanced	Proposed Rationale	Trade-off/Limitation
B-ring 4'-OH / 3',4'-diOH	Antioxidant, Nrf2 activation, Apoptosis induction	H-bond donation, redox activity, metal chelation	High metabolic lability (O-glucuronidation), potential pro-oxidant toxicity.
B-ring 4'-OCH_3	Metabolic stability, Cell cycle arrest (G2/M)	Blocks Phase II metabolism, increases lipophilicity.	May reduce direct antioxidant and some target affinities.
B-ring Halogen (e.g., 4-Cl)	Anti-inflammatory (COX-2), Antimicrobial	Electron withdrawal, increased membrane permeability, altered protein binding.	Can increase cytotoxicity/off-target effects.

A-ring 2'-OH	NF-κB inhibition, Tubulin binding	Intramolecular H-bond stabilizes planar conformation.	Can increase susceptibility to oxidation.
Intact α,β-Unsaturated Ketone	Michael acceptor targets (IKK, Keap1, Tubulin)	Electrophilicity for covalent modification or strong non-covalent interaction.	Reactivity linked to potential off-target effects and toxicity.
Prenylation on B-ring	Cytotoxicity (some cancers), Lipophilicity	Greatly increased lipophilicity and membrane partitioning.	Often drastically reduced aqueous solubility and complex metabolism.

6. Recent Advances and Clinical Perspectives

The course of chalcone studies has obviously been transformed into either a phenomenological analysis of natural isolates to a complex, goal-oriented engineering project. In this last analytical part the present day scene is investigated, the derivatives that are being the most promising as soon as they reach clinical practice are reviewed, the intellectual property that defines the subject, the disillusioning truth of human trials and the considerations of toxicology that matter above all. Here the multidisciplinary problem of drug development is placed into most focussed perspective that requires a balance between potent in-vitro activity and the realities of in-vivo safety, in-vivo metabolism and in-vivo therapeutic utility.

6.1. Notable Chalcone Derivatives in Preclinical Development

Synthetic optimisation of chalcones is a highly fruitful area of preclinical pipeline development to address the drawbacks of their natural counterparts. One of the prevailing trends is the strategic use of bioisosteric replacements and heterocyclic rings to improve target specificity and drug-like characteristics.

One of the most remarkable ones is a derivative of chalcones, MET-3-113, which is a dual polymerisation and efflux pump (P-gp) inhibitor of tubulin and a fluorinated mediator. This mechanism not only has potent cytotoxic effects on a wide range of cancers but also circumvents multidrug resistance (MDR) common to most chemotherapeutics and this is shown to have remarkable activity in paclitaxel-resistant lung cancer xenografts [67]. HNK -chalcone hybrids, in which the natural sesquiterpene hinokitiol reacts with a chalcone unit, are also considered innovative. These hybrids are synergistically anti-proliferative and have shown strong action with triple-negative

breast cancer (TNBC) through induction of mitochondrial apoptosis at the same time inhibiting metastasis in vivo [68].

In addition to oncology, chalcones are currently being designed in metabolic and neurodegenerative diseases. CH -08 is a synthetic chalcone containing a pyridinyl B -ring that has proven to be a potent and selective monoamine oxidase -B (MAO -B) inhibitor that has better neuroprotective properties in MPTP models of Parkinsonism than the standard drug selegiline, and has limited affinity for MAO -A, thereby minimizing chances of hypertensive crisis (the so-called cheese effect) [69].

6.2. Patented Chalcone-Based Compounds and Formulations

1. This is evident in the intellectual property environment that has been strategically oriented on new chemical entities and superior delivery systems. According to recent patents (2018-2023), the following themes may be identified:
2. Combinations Therapies: Patent WO2021185889A1 safeguards an immunomodulatory regimen of a particular methoxychalcone analogue, along with a PD-1/PD-L1 immune checkpoint inhibitor, to treat solid tumours, which is an early move towards immuno-oncological uses [70].
3. Bioavailability Formulation Patents: Many patents seek to deal with low solubility and stability. An example is US11426421B2, which uses preclinical species and a poorly soluble antidiabetic chalcone to report a greater than 5-fold improvement in oral bioavailability as a solid dispersion formulation using polyvinylpyrrolidone -vinyl acetate copolymer (PVP-VA) [71].
4. Prodrug Strategies: Patent EP3892267A1 is a proposal concerning a family of phosphate ester prodrug versions of cytotoxic chalcones. Such prodrugs are highly water soluble so that they can be delivered intravenously and are specifically hydrolyzed to their active aglycone by alkaline phosphatase, an enzyme abundantly expressed in tumour cells and the tumour microenvironment [72].

6.3. Chalcones in Clinical Trials: Current Status

Pure chalcone entities have been translated into clinical use with caution and limited success, similar to the deep-rooted issues of the natural-product-derived drug development. The reviewed primary clinical trial registries (ClinicalTrials.gov and the EU Clinical Trials Register) indicate a scanty, but still developing, picture. There is no chalcone-based novel chemical entity that has progressed to Phase III trials as of early 2024. The most advanced is the Coulbamid (SPIINO), a synthetic chalcone that was developed to treat sickle cell disease and has been taken to Phase II due to its anti-sickling and anti-inflammatory properties, but its development does not seem to be progressing. Another prominent study in progress is a Phase I/II study (NCT04323280)

that is researching a topical chalcone-based gel (AP-618), which serves as the treatment of genital warts caused by human papillomavirus by utilizing antiviral and immunomodulatory effects of the compound [73].
Survey: The majority of human studies that utilize chalcones are dietary intervention or pharmacokinetic studies that use natural extracts that contain chalcones (e.g. licorice, hops). Although useful in the determination of safety of consumption, these studies are not rigorous therapeutic efficacy experiments of particular disease conditions. This discontinuity indicates a very important bottleneck: the transfer of convincing preclinical results in rodent models to the start of effective, well-structured clinical experiments in humans.

6.4. Toxicological Considerations and Safety Profile

High reactivity as the basis of the pharmacodynamic activity of chalcones also creates toxicological issues. It is necessary to have an objective assessment with the difference between the effects observed at the pharmacological doses and the safety of dietary consumption. The most common organ toxicity reported during the preclinical studies is hepatotoxicity. Some synthetic chalcones, especially those that have strong Michael-acceptor properties and lipophilicity, have the potential to empty hepatic stores of glutathione (GSH) and cause oxidative stress, increasing hepatic enzymes. The structure-toxicity associations show that dihydroxylated (catechol) patterns and unsubstituted reactive enones are associated with increased hepatotoxic activity, and methoxylation progressively counters the hepatotoxic activity [74].
Phototoxicity is also a known issue particularly with chalcones containing long conjugation. When exposed to UVA, these compounds can fill excited states that produce singlet oxygen or other reactive species that can cause damage to cellular membranes and DNA with direct consequences that may be applied to the development of topical formulations.
However, this toxicity needs to be put into context. A large number of dietary chalcones (e.g., phloretin, isoliquiritigenin) have superior safety profiles in nutritional concentrations. Besides, the pro-oxidant ability that could be cytotoxic in a normal cell is often specifically targeted to cancer cells which normally aren't under increased basal oxidative stress. This observation implies that there is a therapeutic window. The chronic effects should be demonstrated in the long-term as the results of in-depth toxicogenomic studies to detect predictive biomarkers of adverse events [75].

7. Future Directions and Conclusion

The history of the chalcone scaffold as a core botanical metabolite to a core drug discovery scaffold is an interesting story of drug discovery.
As revealed below, the synthetic accessibility, potent polypharmacological bioactivity, and usefulness as a biosynthetic precursor that are inherent to this structure are

counterbalanced by both serious pharmacokinetic and translational drawbacks. The future direction should thus not be based on the chance but instead be an active, intelligent compilation of these molecules with the use of the latest scientific models to overcome historical limitations. This final part outlines the most promising research directions in the future, placing them in the context of the required steps to transform the undeniable potential into clinical reality.

7.1. Integration with Systems Biology and Omics Technologies

The classical paradigm of reductionism in which the effects of chalcones are limited to isolated targets fails to reflect the system level effects of the compound. The future research needs to combine the transcriptomics, proteomics, and metabolomics in order to develop holistic and mechanistic networks. Indicatively, by using RNA-seq and phosphoproteomics on cells exposed to a lead chalcone analog, it is possible to identify new off-target pathways and biomarker accolades of both efficacy and toxicity [77]. This method is particularly vital to the contextual activity of these multi-target agents; their activity under normoxic and hypoxic tumour microenvironment, or healthy and inflamed tissues is also likely to be very different. Also, pharmacometabolomics would be able to determine inter-individual variation in response by the unique metabolic phenotype of a patient, thus getting personalized treatment. Therefore, a systems biology paradigm will propel the field into a list of proteins affected further to a predictive perspective of cellular reprogramming by chalcone.

7.2. Chalcones as Multi-Target Directed Ligands (MTDLs)

Complex, multifactorial diseases like the Alzheimer disease, cancer, and the metabolic syndrome have not been very successful in the one drug, one target paradigm. Chalcones, having their inherent ability to interact with multiple targets, are excellent candidates of rational MTDL design. Developments are being made in the move toward incidental polypharmacology to intentional one, by use of structure-based design and computational modeling to design hybrid molecules that optimally interact with a pre-defined set of disease-relevant targets. The design of chalcone derivatives, which at the same time inhibit acetylcholinesterase (AChE), 2 sub -secretase (BACE1), and have the ability to serve as metal-chelating agents in treating Alzheimer, is a compelling example [78]. The key issue will be how to balance affinity in various targets and maintain the drug-like nature in general and not be too promiscuous to cause adverse effects.

7.3. Nanotechnology for Targeted Delivery

In order to surmount bioavailability and selectivity challenges in a decisive fashion, the future of chalcone therapeutics is directly connected to the advanced nanocarrier systems. The tumour accumulation can be significantly improved by passive targeting by the enhanced permeability and retention (EPR) effect and active targeting by surface-grafted ligands (e.g., folic acid, RGD peptides). Next-generation stimuli-responsible nanocarriers have been demonstrated to be particularly optimized to chalcones, however,

and redox-responsible systems have been demonstrated to take advantage of glutathione (GSH) levels high in cancer cells to induce intracellular release [79].
Combination delivery is also made easy through nanotechnology. The ability to co-deliver a chalcone with a chemotherapeutic agent (e.g. doxorubicin) or immune-checkpoint inhibitor in one and the same engineered particle can coordinate pharmacokinetics and maximize the synergistic activity at the same target cell, which is superior to the efficacy of free-drug combinations. The current research on liposomal and polymeric micelle formulations of methoxylated chalcones already revealed that tumour growth inhibition in vivo was ten times through than when the drug was applied as a free drug, and the hepatotoxicity was significantly reduced [80].

7.4. Concluding Remarks: From Plant Precursor to Pharmaceutical Lead

To sum it up, chalcone scaffold has managed to pass a significant conceptual transformation. It is no longer perceived as a temporary plant metabolite or a simple precursor to flavonoids, but rather as a distributed, multifaceted and engineerable pharmacophore having pervasive therapeutic applicability An intersectional sound synthetic chemistry, extensive SAR knowledge and mechanistic pharmacology has resulted in a sequence of maximised derivatives with striking preclinical effects in a wide range of pathologies.

However, the biggest issue in the sector has been the ability to translate a lead pharmaceutically viable into approved drug. This translational gap can only be overcome by further in vitro work of novel derivatives; instead it will require a dedicated effort toward solving the underlying issues: improving target selectivity via rational design, improving adequate and targeted delivery via nanomedicine, and performing rigorous predictive toxicology. The candidates that represent these solutions are to be placed in the clinical pipeline.

There is a somewhat inter-disciplinary future in chalcone research. It requires the efforts of synthetic chemists, computational biologists, pharmaceutical developers, and clinical investigators. Through the incorporation of systems-level analysis, rational multi-target design, and intelligent delivery technologies, the chalcone scaffold will hold the promise of being realised within the next decade, thus transforming these ancient plant compounds into modern, effective and safe therapeutics of some of the most serious human afflictions. The history of the scaffold, its roots as a plant precursor, up to the discovery of the scaffold as a pharmaceutical workhorse, have now been simply traced.

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Chapter 4: Solvent-Free and Eco-Friendly Synthesis of Schiff Bases and Imines

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Abstract

The current conventional synthesis of Schiff bases and imines heavily relies on organic solvents that lead to a lot of waste and that have adverse effects to the environment. This chapter has been critically reviewed to look at solvent-free methodologies as a new paradigm in green chemistry. It argues that solvent removal is not only a limitation but is a strategic benefit not only because it enables the chemical reactions to be more rapid, cleaner, and efficient. The argument begins with an introduction of the ubiquitous importance of imines and the need to reform the environment. It goes further to examine the mechanistic basis of reactions in the neat conditions when the extreme molecular proximity and new sources of energy transforms reactivity patterns. A repertoire of protocols that are experimentally demonstrated is given, such as mechanochemical grinding, thermal fusion, catalyst-mediated procedures, and more recent accelerators, e.g. microwave irradiation. They are assessed within the framework of emergent hybrid methods that involve sonochemistry and photoinitiation. Notably, the chapter utilizes quantitative evaluations of environment claims and the problem of scalability and also considers the large scope of substrate as well as the outstanding selectivity benefit of solvent-free procedures. Moreover, it emphasizes the need to incorporate these processes into operational materials and the importance of these processes as intermediates in tandem multicomponent reactions. In conclusion, giving advice to researchers and a future outlook, the chapter recommends solvent-free thinking should be an effective part of the normal synthetic repertoire and states that there needs to be a transition to intrinsic sustainability in molecular construction.

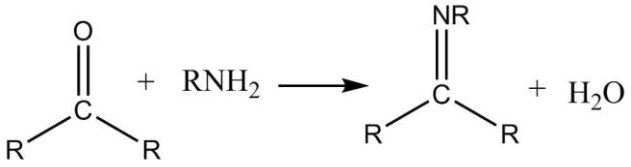
Keywords: Imine, Schiff bases, aldehyde ketone, green chemistry, mechanochemistry, solvent free synthesis

1. Introduction

1.1 Schiff Bases and Imines: Ubiquitous Scaffolds in a Chemist's Toolkit

Go into any synthesis laboratory, be it that of someone designing new pharmaceuticals or that of one designing new materials, and you are likely to find a chemist working with the imine functional group. These compounds, which are the product of an aldehyde and a primary amine, are often referred to as Schiff bases because these compounds contain a carbon-nitrogen double bond (C=N), which is much more than a footnote in organic chemistry textbooks[1]. Basically, they are among the most versatile and essential molecular connectors to the discipline.

They are important due to a harmonious simplicity and reactivity. An example of such a condensation reaction is the formation of an imine, which is normally formed by the condensation of a carbonyl group with an amine, and the by-product is a water molecule. This simple procedure is deceptive as to the depth of the usefulness of the product. C=N bond is a strategic point of synthesis. It is stable to be separated and defined, but reactive enough to act as access to a huge range of nitrogen-containing target molecules, such as amines, heterocycles, such as aziridines and b-lactams, as well as more complex natural product analogs.



(Schiff base)

In addition to their use as synthetic intermediates, imines and Schiff bases are end products of interesting intrinsic worth. They are preferred pharmacophors in medicinal chemistry.[2]. Most of them demonstrate a broad array of biological functions including antimicrobial, anticancer, antiviral, and anti-inflammatory and are the focus of drug discovery programs[2]. In materials science, they have basic coordinating properties of metals. The complexes of the metal of the schiff bases are the workhorses of catalysis, models of metalloenzyme activity, and components of design of the magnetic materials, sensors, and dyes [3]. They are reversibly formed and are the foundation of the area of dynamic covalent chemistry, which allows them to form self-healing polymers and adaptive molecular systems.

1.2 The Hidden Cost of Convenience: Environmental Toll of Conventional Solvent-Based Methods

The traditional laboratory reaction sequence to prepare an imine has a long and well-known history; dissolve the carbonyl group in a reactive organic solvent methanol, dichloromethane, toluene, chloroform add a dehydrating agent or acid catalyst and heat under reflux. It is a sure technique, which is taught to all undergraduate students, and ingrained in the chemical mentality. What makes it convenient camouflages a very large

and cumulative environmental debt that the field can no longer afford to take lightly anymore.[4].

The main guilty party is the solvent itself. In a conventional synthesis of an imine, the solvent is a passive medium, which makes up a large part of the total reaction mass, frequently 90 per cent or more of the total mass. However, its postmortem is not inactive. The environmental ratios are not pleasant. These processes may have astronomically high values of the E-factor (Environmental Factor), which is defined as the ratio of waste to the desired product. Though a zero E-factor is optimum, fine chemical and pharmaceutical syntheses commonly report E-factors of 5-100 with the solvent waste being the most prominent contributor. Likewise, the Process Mass Intensity (PMI) ratio which is the amount of mass consumed per mass of product speaks volumes of resource wastage, in which kilograms of materials are consumed to make grams of product[6].

The wastes produced are not harmless. Dichloromethane and chloroform are examples of such persistent environmental pollutants, which are highly toxic ozone-depleting substances. Tolus and benzene are aromatic hydrocarbons and are very dangerous to health and add to photochemical smog[7]. Distillation is also an energy-consuming process to recover even the workhorse methanol. In both academic and industrial worlds, the aggregate mass of used solvent of such millions of such daily condensations creates a truly huge waste stream, which must either be disposed of at a high cost, incinerated, or subjected to energy-intensive recycling.

This paradigm is finite based. The extraction, refinement and delivery of these solvents has their own significant carbon footprint and environmental impact of its own[7]. The irony of this situation is that chemists will use one liter of petrochemical solvent to carry out a reaction that removes only 18 grams of water. It has given rise to an unsustainable culture of wastage in which the tool has become the major cause of the issue [4-6].

1.3 The Green Chemistry Principles as Our Guiding Compass

In the presence of the grim truth of the traditional synthesis wastes, a revolutionary paradigm is necessary- one that goes beyond the design of environmental protection to the molecular blue print itself. This is where Green Chemistry, a philosophical and practical doctrine as expounded by Anastas and Warner on their Twelve Principles comes in[8]. These principles are not just a checklist, but a rethink in the basic direction of chemical thinking, a shift in thinking towards preventive rather than therapeutic. In the particular case of re-engineering the synthesis of imine, they are an essential guide, and every strategic choice would be directed towards a more sustainable result.

These are some of the values that address the fundamental issues mentioned above. The initial and the most crucial is Prevention: It is better to prevent waste than to treat or to clean up waste after having created them[8].

Related: Principle 5: Safer Solvents and Auxiliaries which advocates the use of innocuous substances is closely related to the concepts proposed above. In cases where the total removal of solvent is not possible, then this principle guides the choice of more

friendly options. However, when it comes to the synthesis of imines, the most beautiful use of this principle is associated with the elimination of the auxiliary reagents, returning to the state of solvents. The high value of Atom Economy (Principle 2) is inherent in a simple condensation; but is often lost in the course of work-up and purification. By comparison, solvent-free methodologies tend to simplify the purification process, and thus maintain such an intrinsic efficiency.

Another, less frequently mentioned source of guidance is based on Principle 6: Design for Energy Efficiency which promotes processes run at a chilly or ambient energy level. Although solvent-free processes that use heat can also be carried out, many reactions by mechanochemical methods or catalyst-enhanced reactions can occur at room temperature, which saves a great deal of energy compared to a long reflux with a solvent. Lastly, the concepts of Catalysis (Principle 9) and Inherently Safer Chemistry (Principle 3) are naturally extended to solvent-free methods with minimal amounts of a non-hazardous catalyst in place of stoichiometric amounts of hazardous reagents.

2. The Premise: Why Go Solvent-Free? Neat Condition Insights of Mechanistic.

The choice to do nothing with the solvent is not just an omission but it is essentially a re-engineering of the reaction milieu. The possibility of reacting neat solids or liquids might be a counterintuitive, even problematic idea to chemists used to the homogeneous environment of solution-phase chemistry.

2.1. Re-examination of the Mechanism: Condensation without Dilution.

The mechanisms of forming imine cannons occur in a solvent mediated environment in a canonical textbook fashion. It takes place in the form of a nucleophilic addition of the amine to the carbonyl and it is accompanied by proton transfer and removal of water. The solvent carries out a number of implicit roles: it dissolves and dilutes the reactants, stabilises charged intermediates (including the tetrahedral intermediate), promotes proton transfers, and usually facilitates azeotropic removal of the resulting water.

In suitable circumstances, this common pattern is reformulated. The greatest transformation is the dramatic increase in the effective molarity of the reactants. In solution, the molecules will be diluted and surrounded by the solvent cages; in a neat mixture, they will be in permanent and close contact. This increased proximity greatly increases the rate of the initial nucleophilic attack because the likelihood that an amine-carbonyl collision will occur successfully is greatly increased.

The position of water changes to being a solvated by-product to being a key physical actor. Water is regularly removed in solution to push the equilibrium toward the formation of products. The removal of water is a physical complication in a neat melt or paste, unless it is removed effectively out of the reaction micro-environment, the water can slow down the reaction or cause hydrolysis of the product. This explains why the addition of a solid desiccant (such as powdered molecular sieves) to a grinding reaction

or the use of mild vacuum or gas purge in a hot neat reaction tend to work so well, disequrying the equilibrium without the presence of a co-distilling solvent.

2.2. The Power of Intimate Proxemies: Molecular Proxemies.

Two main effects are the results of this proximity effect. First, it can trigger drastic rate increases: the reactions that have to be run long hours in reflux often can be finished in minutes under solvent-free grinding or microwave conditions. Second, it has the ability to increase atom economy at the operative level. Since the solvent molecules, or a diffusion process to access the reactants, to take place in side reactions, these reactions are less likely to occur with a neat and highly structured matrix in which the desired bimolecular collision dominates.

2.3. Resolving Problems: The Control of Exotherms and Mixing in Liquid/ Solid Systems.

The hyperactivity of the naked systems poses feasible concerns and hardships that should be given serious consideration. The first issue is related to thermal management. Significant exotherms may be produced by high concentration and reactions rate. It is cooled in solvent by the large thermal mass of the solvent bath, and in a neat reaction, at least when on large scale, it can quickly gain significant heat and loss of control or decomposition or even safety issues may arise.

The second critical problem is to have homogeneous mixing in heterogeneous systems. An example of a typical reaction is the reaction of a solid amine and a liquid aldehyde. The solid can just lie on the bottom of a traditional flask with a magnetic stir bar, and this leads to low conversion. Solvents free chemistry thus requires more advanced mixing strategies including:

- Mechanical grinding: straining touching with shear and compression.
- High-shear stirring: specialised stirrers that are able to work pastes and solids are used.
- Ball milling: in which the mixing and energetic input is provided by the milling balls.
- Intermittent grinding: to scale-up, the reaction mixture may be scraped and re-ground manually or mechanically to get new surfaces exposed.

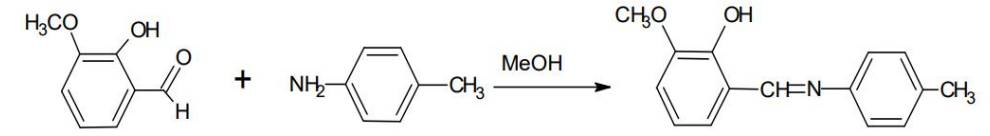
3. The Toolbox: Solvent-Free Synthetic Methodologies.

The process of moving on to more practical use of the theoretical to the practical needs a dependable set of techniques. The chemist without solvents has a wide array of instruments, including raw, near-crude techniques, and those that take advantage of high-tech technology. All tools have distinct operating principles based on the input of energy and molecular organization, but all the tools have in common the need to achieve chemical transformation without the use of a bulk solvent medium. The choice of the

right-tool is dependent on the physical characteristics of the reactants and the magnitude of the reaction as well as the intended result.

3.1. Mechanochemistry

Mechanochemistry in its simplest form is a science of employing mechanical force to produce chemical reactions. This may begin, in the case of solvent-free synthesis, with the most basic of instruments: a mortar and pestle. This method, which is also known as neat grinding or trituration, is used to physically grind solid reactants (sometimes including a liquid reactant or a catalyst additive) to form a homogeneous paste or powder in which a reaction takes place.



2-hydroxy-3-methoxybenzaldehyde *p*-toluidine 2-methoxy-6-{[(4-methylphenyl)imino]methyl}phenol

Case Study: The Audible "Click"

Some mechanochemical reactions cause some non-visual sensory feedback. During the formation of certain metallic coordination polymers or even strong imines, a skilled chemist can even hear a slight but definite audible click as the product is formed. It is thought that this acoustic signal is due to an abrupt phase change in material properties a phase transition between a mushy mixture of reactants to a much harder and more crystalline product network, that emits sound when broken under the pestle.

3.2. Thermal Fusion: Harnessing Controlled Heat

In cases when reactants are low-melting solids or liquids, a potent and simple technique is the use of controlled heat in the absence of solvent with no solvent-thermal fusion. In this method, the reactants are heated in a neat mixture in the presence of the catalytic quantities of an acid and to a temperature capable of bringing the reactants into a homogeneous melt, in which the condensation may proceed rapidly [12].

Applied Reflection: The Art of Finding the “Goldilocks Zone” of Temperature.

Thermal fusion is dependent upon the ability to control temperature precisely, which has been called the search of the Goldilocks Zone [17]. This zone is particular to every reaction system and is delimited by two critical failures:

• **Too Cold:** This is a heterogeneous, unmixed, viscous mixture which forms a mixture in which there is inadequate diffusion of the molecules and the reaction is imperceptibly slow or stagnant.

Too Hot: This causes decomposition of the reactants or the sensitive imine product due to excessive heat and may cause side reactions to occur including condensing the

aldehyde to aldol. Safety hazards are created by violent exotherms or boiling in the extreme cases.

3.3. Neat Reactions with Catalysts Minimal Additives, Maximum Impact.

Whereas certain imine formations can be carried out effectively without a catalyst keeping solely thermal and mechanical conditions, others are favored by the clever employment of a catalyst. Solvents-free paradigm is not necessarily related to the absence of catalysts; it is the perfecting of the role. In this case, the catalyst should be extremely efficient and preferably perfectly incorporated in the solid or molten reaction matrix. A shift occurs in the process of dissolving a catalyst in solvent to the incorporation of the minimal quantity of a strong agent that may operate at the interfaces of neat reactants [18].

Green Catalysts in the limelight And the driver towards sustainability goes to the agents: Scientists have been able to use a variety of types of benign catalysts to carry out solvent-free imine synthesis:

- **Biodegradable Organic Acids:** classic examples include p -toluenesulfonic acid (PTSA) or citric acid in solid form. Presence of a small number of crystals to which the reactants are grounded offers the desired protonation of the carbonyl to speed up the attack of the nucleophilics. They are solid and therefore tend to be present mixed with the product paste but removable through simple aqueous wash during work-up, which is a stark contrast to the neutralisation of large volumes of acidic solvent waste [19].
- **Supported Reagents:** This approach immobilizes the active catalytic species on a high-surface-area solid support, such as silica, alumina, or clay. For instance, **silica-supported sulfuric acid** or **alumina-doped reagents** provide acidic sites while acting as a dispersing agent that increases reactant contact. After the reaction, the supported catalyst can frequently be recovered by simple filtration and potentially regenerated.[17]
- **Natural Clays and Zeolites:** Minerals like **montmorillonite K10** or **kaolin** are cost-effective, non-toxic, and abundant. Inorganic Lewis Acids: Substances with exposed aluminum centres and which have surface hydroxyl groups can readily catalyze the formation of imines. Their structured layers can have the role of nano-reactors, where the reactants are confined and there is a possibility of enhancing selectivity. The inorganic materials used after use have low environmental risk [20].
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3.4. The Modern Accelerator: Microwave-Assisted Solvent-Free Synthesis

Microwave-Assisted solvent-free synthesis of multiple products in solution.

The solvent-free chemistry has been transformed with the introduction of microwave irradiation, which offers a special means of energy provision. Contrary to traditional

heating, where conduction and convection are used to slowly heat a vessel by its periphery, with the help of microwave energy, every molecule within the reaction mass is directly exposed to heat. This is especially useful in neat systems since polar reactants or intermediates are able to absorb a microwave radiation effectively and lead to rapid, uniform, internal heating [10].

The advantages are immense: times of reaction are dramatically decreased, hours turn into minutes or sometimes seconds, energy use is minimised and the speedy heating occasionally results in cleaner reactions because time the reaction can exist to undergo thermal decomposition techniques is minimised.

4. Spotlight on Innovation: Emerging and Hybrid Techniques

Creative adaptation of external sources of energy and intelligent exploitation of solid-state surroundings drive the development of solvent-free synthesis. Along with the technologies of grinding, heat, and microwaves that are already in place, an edge of new and integrative methods is being created. The main principle of solvent minimisation is often combined with some unusual physical phenomenon in these methods to open new reactivities, increase selectivity or further simplify processes.

4.1. Sonochemistry: Using Sound Waves to Stir Molecules at the Source

Sonochemistry is the use of high-intensity ultrasound of chemical reactions (usually 20 1 MHz). This is a transformative technique when no solvent is used, particularly in heterogeneous mixtures of solids and liquids. The main process is the acoustic cavitation: the fast formation, evolvement, and explosive rupture of microscopic bubbles of a liquid phase (which may belong to a range of the neat liquid reactants) [21].

In the collapse, the bubbles produce localised extreme conditions temperatures in excess of 5000 K and pressures of hundreds of atmospheres though in microscopic volumes and over microseconds [21]. This phenomenon has a number of critical effects in a solvent-free imine synthesis using a solid amine and a liquid aldehyde. To begin with, the bubbles bursting cause strong micro-mixing and turbulence, which keep peeling the solid surface and revealing new reactant. Second, the intense local heating can cause reactions at interfaces which would not otherwise take place at the bulk temperature. Lastly, the mechanical effects contribute to the enhancement of mass transfer in the viscous melts.

The main benefit is that it is possible to perform reactions at room temperature or close to the ambient temperature, thus eliminating thermal degradation. As a case in point, when an aromatic aldehyde is present in paste form with a solid amine, and ultrasound is applied in a basic cleaning bath or in a horn-type reactor, the resulting imine can be obtained in high yield within a matter of minutes, even though simple stirring would not be effective [22]. The procedure is especially useful in the scaling of mechanochemical-type reactions, since the ultrasound can be effectively applied to larger volumes in a reactor to overcome the scalability constraints of manual grinding.

4.2. Photoinduced Syntheses: Where Light is the Only Reagent

Photochemical reactions utilize photon energy to promote reactions of molecules to achieve an excited electronic state that supports reaction. In solvent-free conditions, it gives an exceptional elegance of using light, as an energy-specific traceless reagent [23].

Photoinduction may occur in a number of pathways to produce imine. In other instances, the carbonyl group directly becomes excited by light making the group more electrophilic. In most cases, a very small quantity of a photoredox catalyst, whether an organic dye (e.g., eosin Y) or a semiconductor (e.g., TiO 2) is used in the reaction [24]. When visible light is irradiated upon, the catalyst goes to an excited state and has the capability to transfer single electrons with the reactants. It can be useful in bringing together key radical intermediates to allow the imine to be formed under incredibly gentle, often room-temperature conditions make of the use of acid or heat.

Photochemical approaches have high benefits. Photochemical reactions often exhibit greater functionality group tolerance and specific patterns of selectivity that cannot be achieved in thermal reactions. An example of a pragmatic demonstration would be the mixing of an aldehyde, amine and a catalytic weight of TiO 2 on a watch glass and the irradiation by sunlight. The resultant solid-state photocatalytic conversion is remarkably clean and hence, provides a truly green protocol which not only embraces solvent-free reaction but also utilizes solar energy [25]. The biggest issue is how to achieve good penetration of photons through solid or paste-like substance and this may require special designs of reactors or the use of thin films of the reactants.

4.3. The Use of Innocent Auxiliaries: Molecular Sieves, Silica Gel, and Alumina as Reaction Media

- A complex hybrid strategy is the use of laboratory solids not in the form of catalysts but as active or harmless reaction media. These materials, mainly the molecular sieves, silica gel, and alumina, offer environments of high surface area and porosity, which have significant influences on the neat reactions by both physical and weak chemical reactions [26].
- **Molecular Sieves (e.g., 3 A or 4 A):** They are not strictly speaking physical, but are necessary in the sequestration of water when subjected to milling with reactants or used as a bed in thermal reactions. This irreversible adsorption of water alters the equilibrium of the condensing process to the formation of products and commonly avoids the use of more catalysts or azeotropic distillation [27].
- **Silica Gel (SiO_2) & Alumina (Al_2O_3):** In addition to supportive purposes, these materials have high potential to support the pre-concentration and adsorption of organic reactants to the expansive polar surfaces, placing reactants into close proximity. In addition, surface silanol (Si-OH) or aluminol (Al-OH) may confer weak acidic or basic sites, respectively, and hence may catalyze the reaction. Silica gel is slightly acidic and is often used as an intermediary in the formation

of imines with aliphatic amines, and alumina, with its basic nature is very useful in the reaction with less nucleophilic aromatic amines [28].

5. Critical Analysis: Weighing the Green Claims

The deployment of the innovative methodologies is not a matter of passion; it is a problem that requires an open-minded and hard approach. Although the positive effect of solvent-free synthesis on the environment is broadly announced, scientific community needs to question these claims with the help of quantitative data and rational arguments. This critical discourse is not confined to promotional rhetoric but it provides a balanced evaluation that will help to distinguish the apparent benefits and the hidden costs to green strategies.

5.1. Green Metrics in Action: Calculating Atom Economy, E-factor, and Process Mass Intensity for Solvent-Free Protocols

The field uses standardized measurements to enable objective comparison of the qualitative aspects of a process in order to go beyond qualitative green descriptions. These measures are an intriguing story in the framework of imine synthesis.

Atom Economy (AE) is a measure of the percentage of atoms in reactants that are incorporated in the product. The condensation of a carbonyl and an amine to produce an imine and water has a high atom economy (usually over 85 per cent of combinations) because the only by-product is water, which is an ancillary product. This inherent ability of the reaction is not much affected by solvent used; solvent-free conditions, however, do not compromise the AE and instead alleviate the need to protect groups or derivatize agents that are commonly used in complicated solvent-based sequences [5].

Environmental Factor (E-Factor) which is the ratio of the total waste to the product mass illustrates the transformative benefit of solvent-free methods [5]. Traditional solvent-based synthesis has waste, consisting of solvent (the most common component), aqueous washes, and purification media, with E-factors of 50-200 of laboratory-scale processes. Conversely, solvent-free synthesis (such as through grinding) generally gives rise to waste consisting of only a small amount of solvent to extract a product (e.g. 5mL diethyl ether) and the solid auxiliary product. As a result, the E-factors fall within the point of 1 and 5, with the fact that one to two orders of magnitude were reduced and this is the most convincing argument in favor of solvent-free chemistry.

Process Mass Intensity (PMI) which is the ratio of the total mass of resources used to one unit mass of product can give an overall measure of resource efficiency [6]. A solvent-free protocol eliminates the biggest mass contribution to the calculation the solvent. A solvent-based synthesis process could have a PMI of 100 (with 100g of material used to make 1g of product) whereas an optimally designed solvent-free process can be as small as dictated by stoichiometry, typically between 2 and 10.[29].

The use of these metrics forces a shift to evidence. They make the hazy concept of cleaner chemistry a measurable, comparable fact, which overwhelmingly leans towards solvent-free approaches in cases where minimisation of waste is of the primary concern.

5.2. The Energy Balance: Is the Saved Waste Offset by Higher Thermal Input?

The valid criticism of some solvent-free approaches relates to the consumption of energy. Although removal of solvent waste is beneficial, one should look at the whole picture in terms of the life-cycle energy profile. This question is subtle and approach-specific.

- **Thermal Methods (Fusion/Microwave):** One hour of heating a solventless fusion reaction to 100 o C can use less total energy than 12 hours of refluxing a large volume of toluene (bp 111 o C) due to the lower heat capacity of the neat reaction mass. However, the energy intensity (energy / unit time) may increase as a result of heated heating. Microwave energy is directed to reactants in a highly efficient manner however it functions at high power levels but in limited durations. The compromise is clear high-energy and short-duration energy, and long-duration, low-energy heating of a large solvent bath.[10,30].
- **Mechanochemical Methods:** Ball milling spends electrical energy to power the mill. Nevertheless, most of the reactions have been carried out at ambient temperature and therefore no extra thermal input is required. Comparison of milling with solution-based refluxing studies show that the milling technique may be associated with a reduced cumulative energy requirement when the energy of solvent embodied is factored in[31].
- **Ambient Methods (Grinding, Sonication, Photo):** These methods are considered to be gold standard of energy balance. They use low electric power (ultrasound or light sources) or human power (manual grinding), as well as they do not produce any solvent waste, and high thermal energy is not required either.

5.3. Scalability and Reproducibility: From Benchtop Curiosity to Viable Industrial Process

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- **Reproducibility:** In a homogenously stirred a solution, a general assumption is the spatial uniformity. Consistent mixing and heat transfer become a priority in the case of neat solids or pastes, where heterogeneities will easily invalidate experiment fidelity. The particle size of solid reactants is also a critical consideration in the case of manual operations, frequency and pressure of grinding, and the effectiveness of coupling microwave in the event of continuous heating procedures. Procedural documentation therefore cannot be compromised and must go beyond the shallow description of stirredry at room temperature. When these variables are strictly regulated with calibrated equipment such as standardised ball mills, validated

microwave reactors, or known sieve sizes of solids, then reproducibility is enhanced [14].

- **Scalability The Engineering Hurdle.**

  Heat Transfer: The thermally-fusion of a reaction requires precise engineering to avoid hot spots, and also ensures that a potentially viscous melt is uniformly heated, unlike the much easier convective heating of a solution media that can be controlled.

  Mixing: To scale a reaction done in a mortar and pestle to kilogram scale requires industrial equivalents of these machines including extruders, twin screw mixers, or large volume ball mills.Such devices exist, but have different capital costs than traditional reactor vessels.[33].

  Product Isolation: It may be more inconvenient than extractions made between liquids, but the separation of a large bulk of solid product by an auxiliary solid may be necessary; however, it often eliminates the need to perform additional distillations, and thus simplifies further processing of the product.

A Case in Point: Mechanochemistry in Industry.

The problem of scalability is not theoretical in nature. In the pharmaceutical industry, the need to control polymorphs and the elimination of solvent residues of active components has catalyzed the use of mechanochemistry. Continuous, solvent-free co-crystal and API synthesis Tandem extrusion (reactants feed into a hot screw extruder) has been piloted successfully[33]. This fact shows that, given proper engineering, solvent-free fabrication can become more than a laboratory curiosity to an effective, and even better, manufacturing principle of certain applications. The scale direction requires chemists to work in conjunction with process engineers, re-examining the unit operations instead of simply increasing the size of the flasks.

6. The Proof is in the Product: Scope, Limitations, and Structural Diversity

The benefits of theory and green measures are convincing, but the final test of any synthetic procedure is the faithful production of the desired chemical product. In that regard, the limits of solvent-free synthesis should be carefully evaluated: which types of imines can be synthesized under such circumstances? In what areas does it meet restrictions? And what is the nature of the products? This discussion indicates that it is a method which is truly expansive and yet carefully delimited and can yield exquisite results applied to systems which are compatible.

6.1. Taming Volatile Carbonyls: Strategies for Successful Neat Reactions

One of the main practical issues with solvent-free methods is the low-molecular-weight, volatile carbonyls, e.g. formaldehyde, acetaldehyde or propionaldehyde. The solvent, or a mixture of solvents, serves as a buffer in solution, with these reagents present; in a neat

system the high vapour pressure poses a real risk of evaporation before reaction, resulting in poor stoichiometry, poor yields and serious safety or odour concerns[34]. Effective measures have been formulated to check these reagents:

- **Use of Stable Equivalents:** Paraformaldehyde (solid polymer of CH2O) is the most common reagent used to add the unit of formaldehyde. It then depolymerises in situ under controlled, usually thermally-assisted, conditions to give a controlled release of the reactive monomer into the reaction milieu with the amine.[35].
- **Contained Systems:** In the case of a liquid volatile like acetaldehyde, it is necessary to carry out the reaction in a sealed system e.g. a pressure tube or micro wave vial. This physical confinement eliminates any possibility of loss and even the reaction rates can be enhanced as slight autogenous pressure is produced.
- **Adsorption onto a Solid Support:** Hey can be impregnated onto a high-surface-area solid such as silica gel or molecular sieves, and then the volatile liquid can be adsorbed onto it followed by addition of the amine in order to trapp the reagent and create a solid-solid or solid-paste reaction which reduces evaporation.
- **Low-Temperature Protocols:** It makes use of techniques that use temperatures below room temperature, e.g. mechanochemistry at room temperature or sonication, to decrease the vapor pressure of the volatile component, retaining it in the reaction zone.

The Formaldehyde Paradigm: The reaction of the volatile amines (N methyl) and paraformaldehyde to yield N methyl imines is an example of a successful adaptation.. By grinding paraformaldehyde with a primary amine and a catalytic acid, the exothermicity of the reaction often provides the needed energy for depolymerization and imine formation in one pot, yielding the product cleanly without ever handling gaseous formaldehyde.[35]

6.2. Substrate Compatibility: Which Combinations Thrive, and Which Struggle?

Solvent-free conditions are not universally superior for all substrate pairings. Their success depends heavily on the physical and chemical compatibility of the partners.

Combinations That Thrive:

- **Solid Aldehyde + Solid/Liquid Amine:** This is the ideal scenario for mechanochemistry. Crystalline aromatic aldehydes (e.g., 4-nitrobenzaldehyde, salicylaldehyde) react efficiently with various amines upon grinding, often with spectacularly fast kinetics and high yields.[13]
- **Liquid Aldehyde + Liquid Amine:** These are perfect candidates for thermal fusion or microwave-assisted synthesis. The reagents form a homogeneous melt, ensuring excellent contact. Aliphatic aldehydes and amines often perform very well under these conditions.[12]

- **Substrates with Orthogonal Functionality:** Ketones, while less reactive than aldehydes, can be successfully converted to imines under more forcing solvent-free conditions (e.g., prolonged milling or higher-temperature fusion), especially when activated.[37]

Combinations That Struggle:

- **Highly Viscous or Polymeric Intermediates:** If the imine product or an intermediate forms an intractable gum or glass, it can encapsulate unreacted starting materials and halt the reaction.
- **Severe Reactivity Mismatches:** When one reagent is significantly more volatile or more prone to side reactions (e.g. the spontaneous aldol condensation of an aldehyde) in comparison to its counterpart, the lack of dilution may increase its problems. It can thus be the case that controlled addition strategies are necessary even in the neat systems.
- **Substrates Requiring Strict pH Control:** A heterogeneous neat system is challenging to precisely regulate pH like in buffers. Although solid acids or bases can be used, it is difficult to attain the fine, homogeneous conditions that can be attained in an aqueous-organic buffer.

The Case of Amino Acids: A solvent-free synthesis of amino-acid Schiff bases has been shown to be successful. The amino acids are usually in the form of zwitterions which are not soluble in solution. This avoids the necessity to shield the carboxyl group or large amounts of dipolar aprotic solvents like DMF are used[38].

6.3. Stereoselectivity and Product Purity Under Neat Conditions

An even deeper issue is whether the distinct environment of a solvent-free reaction can be used to affect not only yield but also selectivity and purity of products.

Diastereoselectivity: There is the possibility of stereochemical effects caused by the constrained, solvent-free environment when there are chiral centres. The proximity of the molecules within a crystal or a melt can in certain instances select one diastereomeric transition state in preference over the other, which causes selectivity other than that seen in solution[39]. An example is the mechanochemical reaction of chiral amines with prochiral carbonyls, which have been observed to form distinct diastereomeric ratios which is due to the fact that organised molecular assemblies are selectively formed in the solid state.

- **Purity Advantages:** Purity One of the most reliable findings is the remarkable purity of the products of the solvent-free reactions, and especially mechanochemical reactions. The reason is simply beautiful: formed side products tend to have different physical characteristics (e.g., solubility, melting point). These impurities are left on the filter or in the mortar during the neat reaction, and during the following minimal work-up (e.g. a rudimentary rinse with cold solvent).

- **Crystallinity and Polymorph Control:** Crystal-engineering methods of solvent-free crystallisation, especially by mechanical grinding, are potent means of controlling polymorphic behaviour. The mechanical strain may be able to directly transform reactants into a particular, and usually more stable, polymorph of the product. This is of vital importance in pharmaceutical science in which bioavailability and stability of an active pharmaceutical ingredient is determined by its solid form. In other cases, the required polymorph is obtained by performing a neat synthesis without a solvent-mediated transition.[41].

7. Beyond the Synthesis: Connecting Method to Application

The real value of a synthetic methodology is not merely the capability to make complex molecules, but the possibilities that it provides to be used. The fact that solvents have been removed during the production of imines and Schiff bases is particularly beneficial, as it allows the compound itself to be isolated as well as easily converted into functional materials.

7.1. Direct Integration into Functional Materials: Synthesizing Ligands for Catalysis *In Situ*

- Directly Integrating Ligands into Functional Materials. Schiff bases are the most common ligands in coordination chemistry, active sites in a myriad of oxidation, reduction and polymerisation catalysts. The classical pathway - synthesising the ligand, isolating it, purifying it, and reacting it with a metal salt in a second solvent - involves a series of steps and the application of a number of different solvents [42].
- Solvents free methodologies radically change this paradigm. An example of this shift is the one-pot, two step synthesis and concomitant complexation of the product.Here, the aldehyde is first ground against the amine often in the presence of a mild solid acid. The resulting imine is not isolated, but rather some metal precursor (such as a metal acetate or chloride) is added right to the same mortar or reaction vessel, and the process is repeated. [43]

The benefits are overwhelming:

Elimination of Purification: The ligand is used together with its formation, eliminating the necessity of purifying the intermediates which can be prone to air or moisture.

Atomic Efficiency: The ligand precursor consists of all the atoms that are included in the final complex and the only by-product is water.

Improved Material Properties: This direct approach may provide metal complexes inaccessible by solution routes, and present sometimes unique catalytic behaviors or material properties. As an example, solvent-free mechanosynthesis of porous metal-organic frameworks (MOFs) or coordination polymers using Schiff-base ligands have been demonstrated, in which the mechanical force is used to form the ligand and at the same time use it to assemble the network. [44]

7.2. A Step Towards Tandem Reactions: How Solvent-Free Imine Formation Enables One-Pot Multicomponent Processes

The utility of imines is based on dynamic covalent chemistry. The C=N bond is formed and dissociated respectively at equilibrium. In a solvent-free environment, such dynamics is combined with an extreme molecular proximity, thus making it an ideal host of tandem or multicomponent reactions (MCRs). [45]. In this case the imine is not the end product but a temporary intermediate which is then trapped in the same pot by a third reactant. Solvents-free method has the rare benefits of such cascades:

Concentration is Paramount: The effective molarity is high and this enhances the quick formation of imines.

No Dilution, No Problem: The nascent imine is created in a concentrated solution and then the next reaction step can occur without any solvent dilution and thus enhances the chances of a successful reaction with the third component.

Driving Equilibria: Physicochemical techniques can be useful in the shift of sequential equilibria. As an example, a grinding can facilitate the formation of imines, which can be followed by the addition of a nucleophile (say a diketone in a Hantzsch reaction) which can in turn undergo a cyclisation, drawing the whole series to a close. [46]

Illustrative Examples:

The Strecker Synthesis: This is a three-part reaction of an aldehyde, an amine and a source of cyanide to give 1,4-naphthoquinone: It means that the reaction is solvent-free and carried out on a grinding scale. The imine is formed and is instantly reacting with the cyanide ion, which tends to yield more and also take shorter durations because of the good concentration differentials, especially in solution. [47]

Mannich -Type Reactions: Solvent-free production of an iminium ion intermediate (out of an imine) and the addition of a carbon nucleophile is very efficient. Refined grinding conditions to synthesise 20 -amino carbonyl compounds already exist thereby avoiding the aqueous work-ups that are often coupled with traditional Mannich reactions. [48]

Synthesis of Heterocycles: one that is especially important. Quinolines, benzodiazepines and β -lactams can be prepared in one pot through solvent-free protocols where the initial step is the creation of a Schiff base, followed by an intramolecular cyclisation. The neat conditions often inhibit side reactions that afflict the corresponding solution-phase sequences. [49]

8. Conclusion and Future Horizons: Where Do We Go From Here?

The history of solvent-free synthesis of Schiff bases and imines traces a path that allows returning to the physical origin of chemistry and at the same time moves the discipline

towards a sustainable future. This chapter has attempted to trace this topography as a system of individual methods but as a philosophy of molecular building.

8.1. Summarizing the Paradigm Shift: Elegance Through Simplification

The main idea behind this research is that the removal of solvent will not be a restriction but will become an innovation trigger. We have ceased to see the reaction vessel as a place where a uniform solution passes through it and have instead begun to think of the vessel as a stage on which physical forces grinding, focused heat, ultrasound, and light coordinate their presence in a remarkably efficient way to bring molecules into contact with each other. The paradigm shift is shifted to the levels of dilution and dissipation to that of concentration and focus.

The evidence is compelling. The solvent-free processes always have remarkably low E -factors and can transform waste-infested operations into virtually zero-waste processes. Their high reaction rates and purity are based on the fact that close proximity of the molecules exploit the mere physically close proximity, thereby increasing the reaction rate and making the isolation of a product easier. The discoveries of the mechanics have shown that clean processes generate a particular environment, where the effective molarity, interfacial area, and mechanical activation are the factors that predominate the outcome, [12, 13, 39]. The approaches have been proven useful not only in simple model reactions, but in construction of functional metal complexes directly, and is a critical step in simplified multicomponent cascades. [43, 45]

8.2. Open Ends and Horizons: The Search of Universal Protocols.

- The research is still dynamic, and there are many unanswered questions that provide evidence of the future research direction. This is not aimed at determining one ideal process but to achieve a more profound predictive insight that will make solvent-free synthesis a more specifically focused engineering science, bridging the divide between art and process design.
- **Predictive Scalability:** Although there are reported cases of industrial translation.[33] a multimodal framework of predicting and modelling heat and mass transfer of scalable solvent free reactors is essential. How do we convert the violent movement of a mortar and a pestle into an uninterrupted twin- screw extruder? The lack of connection between chemistry and the advanced process engineering needs to be filled in by conducting a research to prove the good principles of scale-up.
- **In Situ Reaction Monitoring:** Sampling in solution is easy, but realize time monitoring of either grinding or melt formation in the solid state is difficult.It is essential to use in-line methods of analysis, including Raman spectroscopy, X-

ray diffraction, and calorimetry with milling or heating apparatus, more extensively ([53]). These strategies will open the door to kinetic and mechanistic knowledge to allow the analysis of endpoints to be replaced with an in-depth understanding of the processes.

- **The Limits of Compatibility:** There is need to map out systematic reaction phase diagrams. What are the specific conditions of reactant physical state (solid, liquid, eutectic), polarity and mechanical properties under which a particular solvent-free method is successful or not? The approach of machine learning, fed with massive datasets of solvent-free results, could start predicting optimal conditions of untried combinations of substrates ([54]).
- **Energy Life-Cycle Analysis (LCA):** Comparative LCA studies are necessary, which are rigorous and quantitative in nature to determine the overall environmental footprint of solvent-free and optimised solvent-based processes, i.e. the extraction of raw materials to the disposal of the waste products. These are the analyses that will give conclusive data on how to have an industry adopt it and make policy.

8.3. A Personal Vision: Integrating Solvent-Free Thinking into the Broader Chemical Lexicon

I am a researcher who has smelled the sickly smell of halogenated solvents as well as heard the pleasant grind of a neat grind; therefore I do not see just lab practices. I believe that the values that are promoted in this chapter will become a staple of chemical education and practice.

This educational upgrade consists of the use of mechanochemistry and solvenfree thermal reactions to supplement the conventional reflux in the undergraduate labs. Even at the first level of chemical training, a higher level of intuition of molecular behaviour and waste consciousness is possible by permitting students to mechanically manipulate the pestle, not just to simply visualise the reaction under a condenser. ([55]).

Solvents-free synthesis is likely to go beyond the present niche as a green option and become a part of the mainstream of chemical practice. It is an evolution of our scientific attitude--a recognition that the really efficient thing is not only the beauty of the molecular structure thus made, but how wisely and conscientiously he makes it. There is only one way ahead: to keep developing such techniques, to ask the difficult questions of scalability and mechanism, and to teach the next generation that the strongest reaction medium is sometimes no medium at all

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Chapter 5: Pharmacoepidemiology and Real-World Evidence: Understanding Drug Use Beyond Individual Patients

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Abstract

It is a traditional approach to the bedside vigilance as the main anchor of drug safety, and the systematic development of this safety paradigm presupposes the panoramic view of the whole population. The given chapter has gone into the area of pharmacoepidemiology and real-world evidence (RWE) and thus has gone out of the scope of controlled trials and single-case adverse event reports to shed light on the area of medication use patterns and comorbid outcomes in a routine clinical setting. The study of drug utilization is able to show the prescribing patterns thus revealing healthcare behaviour and the systemic risks. With the harvesting of a variety of reservoirs of real-life data (e.g., electronic health records and patient registries) useful evidence is created that can be used to identify safety signals across populations, identify risks in heterogeneous patient groups and influence clinical guidelines, regulatory frameworks and health policy decisions. In addition, the expanding role of clinical pharmacists is highlighted; these professionals serve as the key bridges between the data on population level and the work with particular patients. Lastly, the manuscript reflects on the future trends, such as big-data analytics and realistic trial designs and incorporation of pharmacogenomics to optimize personalized risk prediction. Altogether, pharmacoepidemiology and RWE act as supplements to bedside vigilance, which contributes to a proactive approach to ensuring the safety and effectiveness of drugs to everyone.

Keywords: Pharmacoepidemiology, Real-World Evidence, Drug Utilization Studies, Post-Marketing Surveillance, Comparative Effectiveness, Healthcare Policy

1. Introduction

The chapter purposely extends the focus past the boundaries of the bedside of a single patient and the narrow walls of a clinical study, to consider the broad view of medication usage among groups. Although the previous chapter suggested that the attentive clinician is the source of drug safety, this chapter theorizes the systematic enhancement of drug safety, as a result of the scientific study of the drug use in the daily clinical practice. Pharmacoepidemiology and real, world evidence (RWE) are the coexistentialistic theories that guide the practitioner through this complex world and the letter of the laws to answer those several questions regarding the field of medicine that are beyond the possibilities of clinical trials. It's real and stuff, not just academic. It's a key ingredient of modern pharmacovigilance, healthcare policy, and the attempt to make medication safer and more effective for everyone. [1]

1. Why Individual Safety Data Is Not Enough

Randomised controlled trial (RCT) is the cornerstone premise for drug development. RCTs by their very nature focus on answering a single, most important question: whether the new drug is effective and safe enough compared to a placebo or standard therapy, when tested under ideal, highly controlled conditions. It is actually a weakness of the study's ability to generalise the results that its main strength is its internal validity. Randomised controlled trials (RCTs) are usually done on a small, carefully selected, and homogenous group of patients. Patients with major comorbidities, multiple medications, very young or very old age, or different racial and ethnic backgrounds are often not included in the trials. [2,3] Therefore, once a drug has been approved and is launched into the market, it is given to a patient population that is a great deal more complex, diverse, and less monitored than the one in which it was tested. Side effects that are rare, occur after a long time, or are related to vulnerable subgroups may not be seen at all until a very large number of patients have been treated. [4]

One of the key post, marketing surveillance methods is spontaneous reporting systems like national pharmacovigilance databases. They are indispensable in identifying rare, serious, and unexpected adverse drug reactions (ADRs). These systems, however, are inherently passive and face the major issues of significant underreporting, inconsistent data quality, and not having denominator data (i.e., the total number of patients exposed to the drug). [5] A case of liver failure linked to a new antibiotic is a worrying development. However, without knowing the number of patients who have been treated with the antibiotic, it is not possible to ascertain whether the incidence rate is higher than the normal rate in the population. This mechanism is really good at coming up with ideas for the possible safety signals, but it does not have the quantitative testing capabilities to verify these ideas. What was initially a very narrow, trial-based, "Is this medicine safe?" question, now changes into a broader, practice, based, "How is this medicine really used, and what are its effects in regular care?" This change of perspective has led to the necessity of transforming individual case studies into population, level studies. [6] Moreover, it is not sufficient to focus only on the drug; in fact, one has to comprehend

the entire situation of the drug usage, i.e., which patients are treated with it, what are the dosages and duration are, what the combinations with other drugs are, and the final real-world results. This is what pharmacoepidemiology is all about.

2. Pharmacoepidemiology as the Science of Real Practice

Pharmacoepidemiology is the study of drugs in large, well, defined populations by using epidemiological principles and methods. It is a thorough investigation of the usage of medicines and the results of such usage in an uncontrolled, complicated environment of routine care. Its key elements are the drug (exposure), the health event (outcome, which can be either beneficial or harmful), and the analysis of links between them while simultaneously controlling for confounding variables such as age, disease severity, and other treatments. Pharmacoepidemiologists mainly use observational study designs such as cohort and case-control studies. In contrast to RCTs, researchers do not assign treatments; instead, they observe and analyse the decisions of clinicians and patients. [8,9] This naturally brings about problems, especially the risk of confounding by indication (where the reason for prescribing the drug is itself associated with the outcome), but advanced statistical techniques and meticulous study planning can help lessen these biases. Observational evidence has its value mainly in its external validity or generalizability. It basically gives us the picture of drug use outcomes in real clinical settings where there is the full influence of the natural variability and complexity. A case in point is the fast gathering of real, world evidence on COVID, 19 vaccines. On one hand, the viral vector vaccines' efficacy and short, term safety was ascertained by RCTs. On the other hand, pharmacoepidemiological studies that utilized real, world data kept confirming the vaccines' effectiveness, monitoring very rare adverse events, and determining their impact in different population subgroups and variants. [10,11] EHRs and national registries played a key role in first pinpointing and then measuring very rare risks, e.g., myocarditis after mRNA vaccines in young males, and subsequently they verified the vaccines' benefit, risk balance being highly favourable to the general population. Such work could not have been accomplished within the time span or scope of a traditional clinical trial.

Characteristic	Randomised Controlled Trial (RCT)	Pharmacoepidemiological Study
Primary Question	Efficacy and safety under ideal conditions (Can it work?)	Effectiveness and safety in routine practice (Does it work?)
Setting	Controlled, experiment	experimental Uncontrolled
Patient Population	Selected, uniform, limited size	Uniform, representative of users, very large
Data Source	Prospective research data collection	Retrospective or prospective analysis of routine care data
Key Strength	High internal validity (establishes causality)	High external validity (generalizable to the real world)
Key Limitation	Low generalisability to broad populations	Potential for confounding and bias
Time Horizon	Fixed, usually short-to-medium term	Can assess long-term outcomes and delayed effects
Primary Output	Definitive evidence for regulatory approval	Hypotheses generation, signal evaluation, and post-marketing surveillance

Table 1: Contrasting Evidence from Clinical Trials and Pharmacoepidemiology [4,7,10]

3. Drug Utilisation Studies: Reading the Prescribing Story

One needs to study drug usage patterns before evaluating the effects. Drug utilisation studies (DUS) are essential to pharmacoepidemiology and primarily deal with the marketing, distribution, prescription, and use of medicines in the general population. These studies go beyond analysing single prescriptions to looking at the total pattern of usage and thus, answering the questions: who uses which drugs, when, where, and in what amounts. Prescribing patterns are an extremely indicative tool of how the healthcare system works, whether or not clinical guidelines are followed, and possibly, the extent of irrational therapy. [12,13] For example, a geographical analysis may show a large difference in prescribing the expensive novel anticoagulants, which at least in part may be explained by varying access or different local formulary policies. Findings may include the excessive use of antibiotics for viral infections a major factor in

antimicrobial resistance or the use of antipsychotics as a means of sedation in elderly patients with dementia. [14]

Critically, drug utilization research functions as an early warning system. A sharp and unaccounted increase in the dispensing of a particular opioid or benzodiazepine in an area can also be an indicator of impending misuse or diversion even before it will be reflected in emergency department data or overdose rates [15]. Through tracking this, healthcare systems can be proactive in addressing educational programs, auditing prescriber behaviour and through stewardship programmes. DUS provides the essential denominator and context for safety studies; you cannot interpret an ADR signal without understanding the underlying exposure

Study Type	**Primary Purpose**	**Example Metrics/Outcomes**
Quantitative /Descriptive	To measure the volume and cost of drug use in a population.	Defined Daily Doses (DDD) per 1000 inhabitants per day, cost analysis, and market share.
Qualitative	To understand the reasons behind prescribing decisions and patient adherence.	Prescriber interviews, patient focus groups, and analysis of clinical reasoning.
Evaluative/Outcome-Oriented	To assess if drug use is appropriate, effective, and safe according to guidelines.	Percentage of prescriptions compliant with guidelines, rates of therapeutic duplication or contraindicated combinations.
Time-Series/Trend Analysis	To monitor changes in prescribing patterns over time, often in response to an intervention.	Prescribing rates before and after a safety warning, guideline publication, or policy change.

Table 2: Common Types and Purposes of Drug Utilisation Studies **[16,17]**

4. Real-World Data to Real-World Evidence

The main resource of modern pharmacoepidemiology is real, world data (RWD). These are data about patient health status and healthcare delivery that are routinely collected from various sources. Converting these raw data into clinically useful insights by analysis and interpretation is how real, world evidence (RWE) is generated.

RWD primary sources are:

- **Administrative Claims Data:** They are generated for billing purposes and consist of very detailed records of prescriptions dispensed, medical procedures,

and diagnoses (registered as ICD, 10, etc.). Such datasets provide longitudinal data on millions of patients. However, they do not have detailed clinical information (e.g., lab results, disease severity). [17]

- **Electronic Health Records (EHRs):** Digital versions of patient charts generated during the course of regular care. They include a wealth of clinical information physician's notes, lab test results, vital signs but the format may be unstructured and vary widely from one healthcare system to another. [18]
- **Disease and Product Registries:** Carefully designed and executed collections of data on patients with a particular condition (e. g., cancer, rheumatoid arthritis) or who are using a particular medical product. The primary purpose is research, and these registries often comprise high, quality, standardized outcome measures. [19]
- **Patient-Generated Data:** Data from wearable devices, health apps, and patient-reported outcome surveys are increasingly being collected to help understand symptoms, quality of life, and adherence outside clinical settings.

The effectiveness of RWE depends on its extensive scale, representativeness, and capacity to deal with such issues, which are impractical for RCTs, like long-term safety, comparative effectiveness, and interventions in subpopulations, etc. However, there are quite a few limitations to it. The quality and completeness of the data are quite variable. Confounding, the situation where an unknown factor changes both the treatment choice and the result, is always a problem. Besides, the medical justification for the use is often not precisely documented, it is very challenging to separate the effects of the drug from the natural course of the disease. [20,21] Consequently, RWE is mainly potent, not as a substitute for RCTs, but as a complementary source of evidence, addressing the gaps left by trials.

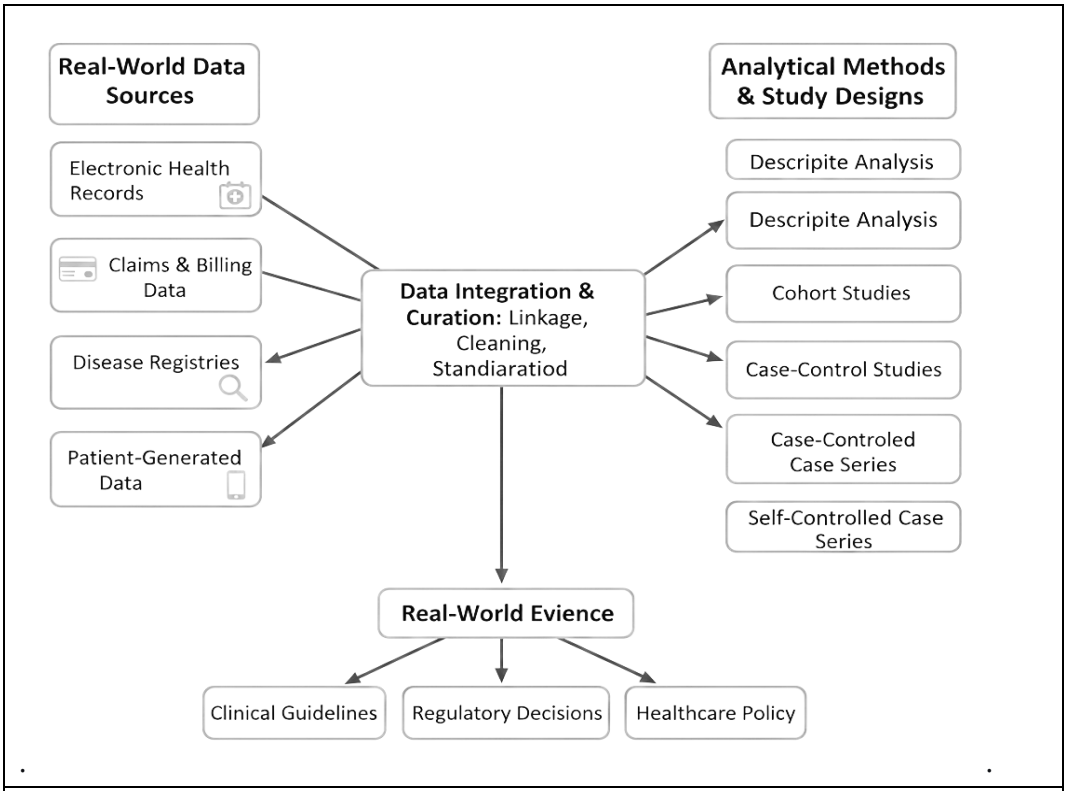

Figure 1: The Transformation of Real-World Data into Evidence for Decision-Making.

5. Connecting Drug Utilisation, Safety, and Outcomes

Pharmacoepidemiology is at its most effective when it combines information about drug exposure with patient outcomes on a population basis. One of the benefits of this approach is that it can uncover drug-patient combinations with a high risk of harm that were not obvious in pre-marketing studies. Generally, a drug utilization study may indicate that a new non, steroidal anti, inflammatory drug (NSAID) is being prescribed mostly to elderly patients. Subsequently, a safety analysis based on linked data might find that this group suffers from a much higher rate of acute kidney injury and gastrointestinal bleeding, relative to younger users or users of other types of pain relief, even when the drug is taken at the recommended doses. [22] Such is a safety concern that can only be identified when it goes to a large scale and in a real-world setting.

Pharmacoepidemiology plays an important role in the quantification of known risks, too. While the label of a drug may signal a certain potential side effect, how often does it actually occur in the clinic? A well, constructed cohort study can give this information by, for instance, explaining how much of the liver enzyme elevation in diabetic patients is the background rate and how much is the additional risk brought by a new glucose-lowering drug. [23] This type of quantitative risk assessment is very important to both

clinicians and patients who have to make treatment decisions. What is more, such studies can look at the level of compliance with risk minimisation measures. For example, after a regulatory safety announcement warning about the increased risk of venous thromboembolism (VTE) with third-generation oral contraceptives, a time series drug utilisation study can check to what extent the prescribing of that product has decreased. Then, a follow-up outcome study can confirm if the incidence of VTE has dropped at the population level. [24] This way, the cycle of signal detection, regulatory intervention, and health outcome entirely changes.

6. Role of Pharmacists in Real-World Evidence Generation

Clinical pharmacists can play an important role in the creation and analysis of real, world evidence not only by collecting data but also by being essential data interpreters and study designers. Pharmacists are in an excellent position to identify clinically significant research questions that may arise from practice. Given their thorough knowledge of pharmacology, therapeutics, and the whole medication use process, they are the ones who can properly formulate such questions. For example, why is there such a large usage of a certain expensive biologic when guidelines suggest step therapy? Does the frequent heart failure readmission relate to specific drug regimens or patient non, compliance? Pharmacists can thus come up with drug utilisation reviews and medication use evaluations that really matter and that are able to assess not only the metrics but also the appropriateness and the outcomes. [25,26]

Most importantly, maybe the pharmacists are the main connection between population data and individual patient care since they can be regarded as the interpreters who turn the results of large cohort studies into understandable messages that can be applied to individual patients. For instance, they can develop and lead antimicrobial or opioid stewardship programs by using local prescribing data, thereby directly applying patient safety and therapy optimisation at the level of the individual, from population, level insights. [27] Pharmacists in institutional settings usually lead or are the main members of the Pharmacy & Therapeutics (P&T) committee, which is the decision-making body regarding the formulary, based on efficacy, safety, and cost, effectiveness, i.e. pharmacy areas where a strong RWE is essential and indispensable. [28]

7. Impact on Policy, Guidelines, and Regulation

The influence of pharmacoepidemiology and RWE extends far beyond the research journal, directly shaping the frameworks that govern the use of medicine. [29]

8. Emerging Directions

The field is being transformed by technological and methodological advances.

Big Data and Advanced Analytics: The mixture of several large-scale treatment guidelines: Clinical practice guidelines are increasingly incorporating real-world evidence (RWE), particularly for long-term management, therapy sequencing, and treatment of complex patient groups that have been excluded from trials. A good example is how real, world effectiveness data obtained through cancer registries can

guide clinical guidelines on the best duration of adjuvant therapy or the treatment of side effects of chemotherapy. [19,20]

Regulatory Decisions: Regulatory agencies such as the U.S. Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) have started to officially accept RWE for supporting decisions related to post, approval safety monitoring, labelling changes, and in some instances, new indications for already approved drugs.RWE played a major role in investigating the cardiovascular risks of diabetes drugs as well as in determining the safety of biosimilars. Moreover, it is at the core of Risk Evaluation and Mitigation Strategies (REMS), drug use is controlled in real, life situations to verify that the benefits of the drug are still greater than the risks. [16,30]

Health Policy and Reimbursement: Payers and health technology assessment (HTA) bodies rely on real-world evidence (RWE) to help them determine coverage and reimbursement decisions. In fact, evidence of comparative effectiveness and cost in real-world populations may be even more relevant to their decision-making than efficacy data from tightly controlled trials. This helps to resolve the often contentious divide between the proven efficacy that regulators require and the demonstrated effectiveness and value that healthcare systems need.

RWD sources (EHRs, genomics, wearables) leads to the generation of "big data" for healthcare. AI and machine learning technologies are used to go through these data sets to find new safety signals, predict patient, risk, and identify the subpopulations that respond differently to treatments. [7,25]

Pragmatic and Platform Trials: These are a combination of research and routine care. Compared to a randomised controlled trial, pragmatic trials contrast treatments in a varied and representative group of patients with minimal interference of protocols hence producing scientifically rigorous evidence, which is highly generalisable. The key in realising the vision of a learning health system is platform trials, which continually compare a series of interventions against a standard control group to chronic conditions [4,7].

Personalized Medicine and Pharmacovigilance: Future trend It is the shift towards predicting risks at the individual level instead of predicting them at the population level. Combining the pharmacoepidemiological data with the knowledge of pharmacogenetics, one can discover the presence of genetic markers predisposing individuals to certain adverse drug reactions and, therefore, develop personalised risk benefit evaluations even without issuing a prescription [22].

9. Conclusion

The two critical aspects of a paradigm shift in drug safety and efficacy relate to pharmacoepidemiology, and real-world evidence. They forge a critical connection between the controlled assurance of the clinical trials and the convoluted reality of clinical practice. Quite to the contrary, this sphere is not a passive observational one, but

rather a powerful trigger of drug consumption change. The final goal is to prescribe safely, which will be obtained by means of methodical interpretation of prescribing patterns, intensive large-scale analysis of outcomes, and extrapolation of the population-level results into point-of-care decision-making. This way we can no longer afford to be reactive towards the pharmacovigilance model which reacts to harm being reported, but rather be proactive and robust in learning, with the overall advantage of all benefiting. The bedside vigilance of clinical pharmacists, which, when applied to a population, is the same as the analytical vigilance of pharmacoepidemiology, is the basis of modern drug safety.

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Chapter 6: solubility enhancement and bioavailability improvement strategies

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Abstract-

Low water solubility is a major limitation to the orally accessible bioavailability and treatment efficacy of a significant proportion of active pharmaceutical agents. In this case, we provide a comprehensive discussion of the existing approaches developed to enhance drug solubility and dissolution rate, thus supporting the enhanced systemic absorption. These approaches are rigorously divided into a pharmaceutical (physical) and chemical one. Pharmaceutical methods involve the reduction of particle size by micronization and nanosuspensions, change of crystal habit by polymorphic and solvate, and pharmacological dispersal by solid dispersions and eutectic system. Chemical methods include pH changes, hydrotropic solubilization, co-crystallization, co-solvency, and salt. To each method we do provide principles, give pharmacological examples of quantifiable bioavailability improvements, and criticize the intrinsic disadvantages, which include physical instability, recrystallization, and the difficulty of the manufacturing process. It has been reaffirmed in the discussion that the solitary approach cannot be universally adequate; the best approach is to have a rational selection process based on the physicochemical nature of the drug, the therapeutic profile of the drug, and scalable production feasibility. This is necessitated by comprehensive familiarity with these techniques, their mechanistic basis and trade-offs that are involved in engineering formulations that are consistently reliable in being translated into dependable and improved in vivo performance..

Key words: Bioavailability improvement, solubility improvement, nanosuspension, solid dispersion, co-crystallization, salt formation, SEDDS, strategies of formulations.

Introduction

A drug with poor bioavailability is defined as having poor aqueous solubility and/or slow dissolution rates in biologic fluids, poor stability of the dissolved drug at physiologic pH, insufficient partition coefficients and consequently, poor permeation through the biomembrane and extensive presystemic metabolism. Thus, to boost the bioavailability of a medicine, several phenomena have been created. Such approaches include: 1. Pharmaceutics approach: altering the drug's formulation, production methods, or physiochemical characteristics without altering its chemical structure.

2. The pharmacokinetic technique, which modifies chemical structure, has a number of drawbacks, including cost, time and the need for repeated chemical analyses, as well as the possibility of precipitation and negative consequences. Furthermore, there is no guarantee that the new entity won't cause another pharmacokinetic issue. 3. Biological approach: with this method, the medicine may be administered by a different route, such as parenteral rather than oral (Bajaj et al., 2011).

PHARMACEUTICS APPROACH ENABLING PHYSICAL MODIFICATION OF DRUGS

(1) PARTICLE SIZE REDUCTION

(a) Micronization:

Micronization enhances solubility via increasing the surface area to drug ratio and expanding the surface area where the pharmaceutical ingredient is capable of disintegrating from the residual drug particle. The Noyes-Whitney equation, which asserts that the surface area of a drug particle directly affects its rate of dissolution, describes this phenomena (Noyes & Whitney, 1897), (Leleux & Williams, 2014). Recently, it came to light that persistently decreasing the size of drug particles into the nanometer range, leading to the development of nanonization techniques, leads to numerous other improvements, such as a faster rates of dissolution that maximizes the drug delivery and absorption to its biological targets, and boosts the bioavailability and effectiveness of drug (Sigfridsson et al., 2011).

(b) Nanosuspension

Heterogeneous aqueous dispersions containing nanosized, hydrophobic drug substances which are stabilised via surfactants are known as nanosuspensions (Jacob et al., 2020).

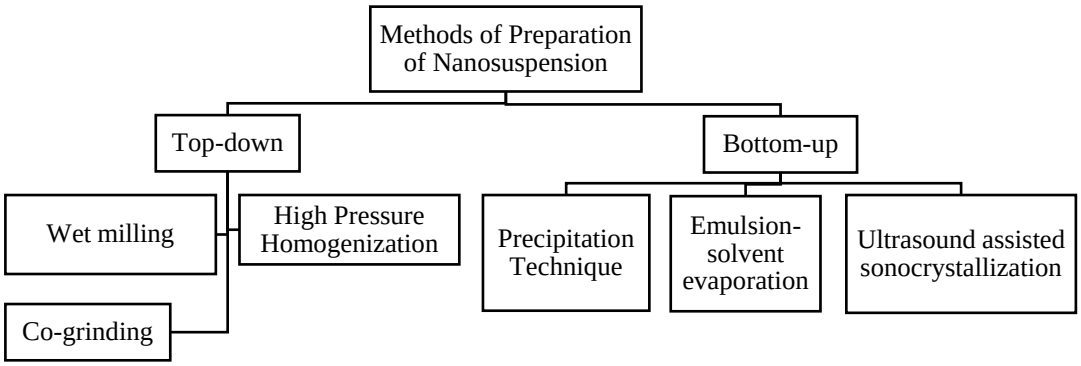

Figure No 1. Methods of Preparation of Nanosuspension

(i) Wet milling: This process uses a media mill or high shear ball mill to create nanosuspensions. Particle attrition and impact both contribute to the size decrease within the drug, stabilizer, and water-filled chamber. It has been shown how to utilize tiny hard zirconium dioxide beads in a wet-milling method to produce uniform-sized nanosuspension (Niwa et al., 2011).

(ii) High Pressure Homogenization: In homogenization, suspension is passed through a valve with a small aperture at extreme pressure (100–1000 bars) to decrease the size of the particles (Liedtke et al., 2000). The microparticles (<25µm) are broken down into the nano-size range by cavitation-induced implosion forces and shock waves in the liquid medium as a result of the static pressure reduction brought on by the abrupt drop in fluid velocity. Moreover, particles having intrinsic crystal defects are fractured by shear forces produced by particle collisions at high velocity (Chavan et al., 2016).

(iii) Dry Co-grinding: Many different polymers and copolymers, such as polyvinyl pyrrolidone, polyethylene glycol, hydroxypropyl methylcellulose (HPMC), sodium dodecyl sulphate, and derivatives of cyclodextrin, were explored as stable nanosuspensions produced via the dry co-grinding method (Wongmekiat et al., 2002).

(iv) Emulsion solvent evaporation technique: Drug is dissolved in an organic solvent or cosolvents to create an emulsion, which is then dispersed in an aqueous phase with a stabilizing surfactant. Nanosuspension is immediately generated when a solvent evaporates quickly under low pressure (Jacob et al., 2020).

(v) Precipitation Technique: Particles of colloidal size range are formed by the aggregation of materials with subcolloidal dimensions. By creating a super-saturated drug solution in a water-miscible organic solvent at the ideal temperature and dispersing it as a minute, measured amount in non-solvent water while swiftly stirring, the approach generated nuclei instantaneously (Patel & Agrawal, 2011).

(vi) Ultrasound assisted sonocrystallization method: It is a newly developed method for creating stable nanosuspension. When used at frequencies between 20 and 100 kHz, ultrasound improves particle size reduction and regulates the size distribution of drugs. Additionally, it is regarded as a successful method for reducing the nucleation and crystallization process (Tran et al., 2014).

(2) MODIFICATION OF CRYSTAL HABIT

(a) Crystal engineering: The design, modeling, synthesis, and use of crystalline solids with a specific and desirable combination of molecules and ions is known as crystal engineering. Utilizing non-covalent interactions between ionic or molecular components to intentionally construct solid-state systems with intriguing optical, magnetic, and electrical properties is recognized as crystal engineering (Fonseca et al., 2018).

(b) Hydrates/solvates: Solvates are molecular adducts that have solvent molecules integrated into their crystal structure. The solvate is referred to as a hydrate whenever the solvent is water (Ritika & Aggarwal, 2012).

(c) Polymorph: The phenomenon known as polymorphs occurs when a molecule has a distinctive crystal structure but identical chemical constituent; as a result, they have distinct physicochemical properties caused by their differing network design and molecular conformations. Numerous drugs can crystallize into different polymorphic forms that enhance solubility because of polymorphism (Bhalani et al., 2022).

(3) DRUG DISPERSION IN CARRIERS

(a) Eutectic Mixtures: Eutectic mixtures can be made by mixing two different drugs with varying solubilities or by combining a drug with an inert carrier, which is typically a highly hydrophilic molecule. In this instance, it is feasible to combine two therapeutically relevant substances into a fixed-dose combination system in addition to improving the solubility of the less-soluble component (Alshaikh et al., 2019), (Bazzo et al., 2019), (Riekes et al., 2016).

(b) Solid Dispersion

The definition of solid dispersion systems is "the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by various method." The matrix is hydrophilic, while the drug is hydrophobic (Chiou & Riegelman, 1971), (Tekade & Yadav, 2020).

(i) Solvent evaporation method

This approach involves dissolving the medicinal product and carrier in an organic solvent. The solvent evaporates once it has completely dissolved. The solid bulk is

crushed, sieved and dried. For example, the solvent evaporation approach was used to generate a solid dispersion of furosemide with eudragits (Rasenack et al., 2003).

(ii) Hot-melt extrusion method

This approach uses a co-rotating twin-screw extruder to prepare solid dispersion, which is made up of the active ingredient and carrier. In the dispersions, the drug concentration is consistently 40% (w/w). The pharmaceutical industry uses the melt extrusion process to prepare a variety of dosage forms, such as sustained-release pellets (Karanth et al., 2006).

(iii) Kneading technique

This procedure involves permeating the carrier with water and transforming it into a paste. Drug is then added and kneaded for particular duration. The kneaded material is then dried and passed through sieve if necessary (Nikghalb et al., 2012).

(iv) Co-precipitation method

An appropriate amount of the drug is introduced to the carrier solution. The system is shielded from light and maintained under magnetic agitation. To prevent the structural water from the inclusion complex from being lost, the precipitate is separated by vacuum filtering and dried at room temperature (Moyano et al., 1997).

(v) Melting method

A mortar and pestle are used to combine the drug and carrier. The mixture is heated at or above each component's melting point to achieve a uniform dispersion. After that, it is cooled to form a solid mass. It is sieved and pulverized. This approach was used to make a solid dispersion of urea and albendazole (Kalaiselvan et al., 2006).

(vi) Co-grinding method

A blender operating at a specific speed is used to physically combine the drug and carrier for a while. The mixture is charged into a vibration ball mill chamber, where steel balls are added. The mixture of powder is ground up. Then the sample is collected and maintained at room temperature in a screw capped glass vial until use. For instance, mannitol with chlordiazepoxide This approach was used to prepare the solid dispersion (Nokhodchi et al., 2005).

(vii) Gel entrapment technique:

A clear, transparent gel is created by dissolving hydroxyl propyl methyl cellulose in an organic solution. After a few minutes of sonication, a drug, for instance, is dissolved in

gel. Under vacuum, the organic solvent evaporates. Mortar is used to reduce the size of solid dispersions, which are then sieved (Bhise & Rajkumar, 2008).

(viii) Spray-drying method

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer (Bakatselou et al., 1991).

(vix) Lyophilization technique:

Heat and mass are transferred to and from the product being prepared during the freeze-drying process. In order to create a lyophilized molecular dispersion, the drug and carrier are co-dissolved in a shared solvent, frozen, and sublimated. This process is known as lyophilization (Betageri & Makarla, 1995).

(X) Melt agglomeration process

This approach has been used to make Solid Dispersion where the binder functions as a carrier. SDs are made by either utilizing a high shear mixer to spray a drug dispersion in molten binder on the heated excipient or by heating the binder, drug, and excipient to a temperature higher than the binder's melting point (Tsinontides et al., 2004)

(4) SOLUBILIZATION BY SURFACTANTS

(a) Microemulsion

Clear, transparent, unstable mixes of two immiscible liquids, such as water and oil, are known as microemulsions. Surfactants generate an interfacial coating that alleviates emulsions (Kumar & Mittal, 1999).

(i) SEDDS

This strategy is used to address low bioavailability issues with highly porous and poorly soluble medicinal compounds. Hydrophobic medicinal compounds can be liquefied in this environment. This mixture is known as a self-emulsification in situ emulsion because the components of the SEDDS come into contact with the gastrointestinal fluid when they are administered in the lumen of the gastrointestinal tract. This results in the formation of a fine micro/nanoemulsion. Additionally, this results in drug solubility, which avoids the hepatic first-pass action by being activated through lymphatic routes. Numerous characteristics of the lipid formulations in vivo have been connected to the bioavailability-improving feature (Rawat et al., 2014).

Processes for self-emulsification:

• Self-nanoemulsifying drug delivery system (SNEDDS)

• Self-micro emulsifying drug delivery system (SMEDDS)

2. CHEMICAL MODIFICATIONS

(1) PH ADJUSTMENT

This has a significant impact on drug solubility. It may affect how soluble drugs are in water. The charge state of the drug molecules can be changed by adjusting the pH of the solution. The solute frequently has little solubility and precipitates out of the solution if the pH of the solution is such that a specific molecule has no net electric charge. The isoelectric point, frequently shortened to IEP, is the pH at which the net charge is neutral (McMorland et al., 1987).

(2) HYDROTROPHY

This is a solubility sensation that allows the excess addition of a second solute to increase the solute's water solubility. In previous reports, non-micelle-forming materials solids or liquids, organic or inorganic that are adept at increasing the solubility of insoluble compounds were referred to as hydrotrophy (Rasool et al., 1991).

(3) CO-CRYSTALLIZATION

The complexes of non-ionic supramolecular materials are called co-crystals. Without changing the chemical structure of APIs, they can be used to solve problems with physical qualities, such as medication solubility, bioavailability, and stability. When two or more distinct molecular units are used to create co-crystals, intermolecular interactions like hydrogen bonding and π–π stacking operate as weak forces. Co-crystallization will alter the molecular interactions and composition of pharmaceutical substances, and it is recognized as an effective way to maximize the drug's properties. Regardless of whether an API belongs to an acidic, basic, or ionizable group, co-crystals will provide a variety of crystallization pathways. Because of their nonionizable functional groups, molecules with modest pharmacological profiles may benefit from this (Patole & Deshpande, 2014).

(4) CO-SOLVENCY

As drug structural complexity increases, its solubility in water drops significantly. A combination of solvents is used to achieve high solubility when a compound's water solubility is significantly lower than its therapeutic dose (Millard et al., 2002).

(5) SALT FORMATION

Compared to their salts, acidic and basic drugs are less soluble in water. Solubility improvement via salt production is the most preferred approach for the development of parenteral administration (Bhalani et al., 2022).

Application

TECHNIQUE-SPECIFIC DRUG APPLICATIONS:

Technique	**Drug Example**	**Disease/Indication**	**Particle size/Change**	**Bioavailability improvement**	**Reference**
Micronization	Griseofulvin	Dermatophyte fungal infections	10-15 µm → 2-4 µm	2-fold bioavailability increase	(Bhalani et al., 2022)
Nanosuspension	Itraconazole	Systemic fungal infections	5-10 µm → 400-600 nm	60-80% bioavailability increase	(Lenhardt et al., 2008)
Hydrates/solvates	Carbamazepine	Epilepsy	Anhydrous vs dihydrate form	Anhydrous dissolves faster than dihydrate	(Brog et al., 2013)
Eutectic Mixtures	Ketoprofen-Nicotinamide	Arthritis, pain	Two crystalline → Eutectic	Dissolution rate increased 4-fold	(Bhalani et al., 2022)
Solid Dispersion	Albendazole	Helminthic infections (anthelmintic)	Crystalline → Eutectic	Dose reduced 400mg → 200mg; 2-fold BA	(Bhalani et al., 2022)
Microemulsion	Propofol	General anesthesia (IV)	Solid → Microemulsion 200-300 nm	Enables IV administration of insoluble drug	(Kalepu & Nekkanti, 2015)
SEDDS	Cyclosporine	Transplant rejection, autoimmune	Solid → Self-emulsifying 100-200 nm droplets	30% BA increase, reduced variability	(Menzel et al., 2018)

pH Adjustment	Ciprofloxacin	Bacterial infections (IV)	Solid → pH-optimized solution (pH 3.5-4.5)	pH-optimized injectable formulation	(McMorland et al., 1986)
Hydrotrophy	Riboflavin	Vitamin B2 deficiency	Solid → Hydrotropic solution	10-fold solubility increase using urea	(Rasool et al., 1991)
Co-crystallization	Meloxicam	Osteoarthritis, rheumatoid arthritis	Crystalline → Co-crystal with aspirin	Improved dissolution, faster onset (30 min)	(Patole & Deshpande, 2014)
Co-solvency	Etoposide	Cancer chemotherapy (IV)	Solid → Solution in PEG/ethanol	IV administration formulation	(Millard et al., 2002)
Salt Formation	Amlodipine besylate	Hypertension, coronary artery disease	Free base → Besylate salt	2-fold dissolution rate enhancement	(Serajuddin, 2007)

CHALLENGES AND LIMITATION

Type/ Technique	Limitation	References
Micronization	Problems with physicochemical stability, such as drug aggregation or a shift in its solid state. Overuse of excipients as stabilizers may alter the pharmacological action and bioavailability of the medication. Bulking care is crucial, especially when handling and transporting.	(Williams et al., 2013)
Nanosuspension	Has an instability issue brought on by Ostwald ripening, agglomeration and crystal formation.	(Brahmankar & Jaiswal, 2019)
Hydrates/solvates	Desolvation/Dehydration, Hygroscopicity and Physical instability	(Healy et al., 2017)

Eutectic Mixtures	High carrier load and Physical instability	(Valenti et al., 2023)
Solid Dispersion	High-energy amorphous drugs have a tendency to recrystallize and transform into low-energy crystal forms. It is necessary for the chosen medication and polymeric matrix to be miscible. One well-known disadvantage is limited stability.	(Baghel et al., 2016)
Microemulsion	Because of their high surfactant/cosurfactant concentration, they should not be administered intravenously.	(Chaudhary et al., 2012)
SEDDS	limited shelf life and poor stability.	(Menzel et al., 2018)
pH Adjustment	The long-term impact on the stability of the medication. The physiological pH distortion and the propensity for precipitation and incompatibility when diluted.	(Jouyban, 2008)
Hydrotrophy	Drugs and hydrotropic agents may have a weak interaction. Water cannot be completely removed because water is used as a solvent. Some hydrotropic agents have limited application due to toxicity.	(Namdev et al., 2022)
Co-crystallization	Complex screening and moisture sensitivity	(Panzade et al., 2024)
Co-solvency	Only a few number of solvents can be used as co-solvents. The possibility of precipitation after dilution. It could change the strength and pH of the buffers in a medication formulation.	(Jouyban, 2008)

Salt Formation	Inappropriate for neutral-digested compounds; limited to weakly basic or acidic medicines. The drug is converted back into its basic or free acid form following oral administration. Restrictions on the selection of ideal salt forms and salt screening.	(Vioglio et al., 2017)

CONCLUSION

Bioavailability enhancement remains a critical challenge in pharmaceutical development, particularly for drugs with poor aqueous solubility, low permeability or extensive first-pass metabolism. This review demonstrates that multiple strategic approaches exist to address these limitations, broadly categorized into pharmaceutical, chemical and biological modifications.

The **pharmaceutics approach** offers the most versatile solutions without altering the drug's chemical structure. Particle size reduction techniques, including micronization and nanosuspension, significantly improve dissolution rates by increasing surface area. Crystal engineering through polymorphs, hydrates and solvates provides alternative solid forms with enhanced solubility profiles. Solid dispersion systems and eutectic mixtures effectively disperse poorly soluble drugs in hydrophilic carriers, achieving substantial bioavailability improvements, as demonstrated by albendazole (2-fold increase with dose reduction). Solubilization strategies using microemulsions and self-emulsifying drug delivery systems (SEDDS/SNEDDS) have proven particularly effective for lipophilic drugs, with cyclosporine showing 30% bioavailability enhancement.

Chemical modifications including pH adjustment, co-crystallization, co-solvency and salt formation offer targeted solutions for specific drug classes. Salt formation remains the preferred method for acidic and basic drugs, while co-crystallization provides opportunities for non-ionizable compounds.

However, each technique presents inherent limitations. Physical instability, manufacturing complexity, high excipient loads and storage challenges are common concerns. Nanosuspensions face Ostwald ripening and aggregation issues, while solid

dispersions are prone to recrystallization. Microemulsions and SEDDS systems often suffer from limited stability and shelf life.

In conclusion, successful bioavailability enhancement requires careful selection and optimization of techniques based on drug properties, therapeutic requirements, and manufacturing feasibility. A thorough understanding of both the advantages and limitations of each approach is essential for rational formulation development and achieving optimal therapeutic outcom

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