RESEARCH PAPER

Heterogeneous Catalysis: A Tool for the Synthesis of Natural Product Analogues

Jagjeet Singh[1]*, Riyaz Ahmed[2]

[1*]P. G. Department of Chemistry G. D. C. Udhampur
[2]P. G. Department of Chemistry G.D.C. Bhadharwah

Abstract
Natural products have historically served as a rich source of biologically active molecules for pharmaceutical and chemical research. However, limitations in natural extraction and structural complexity often restrict their direct application. The development of catalytic strategies has therefore become essential for synthesising natural product analogues with improved biological and physicochemical properties. This review aims to highlight recent advances in heterogeneous catalytic systems used for the synthesis and modification of natural product analogues, emphasising their efficiency, selectivity, and relevance to sustainable chemical synthesis. Recent literature on heterogeneous catalysis was analysed to examine catalytic strategies such as hydrogenation, oxidation, carbon–carbon bond formation, and multicomponent reactions. Emerging catalytic platforms, including single-atom catalysts, metal–organic frameworks, nanostructured catalysts, and photocatalytic systems, were also evaluated. In addition, green chemistry approaches such as solvent-free reactions, microwave-assisted catalysis, and flow chemistry were considered for their role in sustainable synthesis. The analysis indicates that heterogeneous catalysts provide significant advantages in catalyst recyclability, reaction efficiency, and environmental compatibility. Advances in catalyst design have enabled improved selectivity and catalytic performance in complex organic transformations relevant to natural product analogue synthesis. Heterogeneous catalysis offers a promising pathway for developing efficient and sustainable synthetic methodologies. Continued innovation in catalyst design and integration of modern computational tools will further enhance the synthesis of structurally complex and biologically relevant natural product derivatives.

Keywords: Heterogeneous catalysis; Natural product analogues; Green synthesis; Nano catalysts; Sustainable chemistry
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In modern pharmaceuticals and chemical biology, natural products have shown their significant potential. These compounds have a wide range of biological origins such as plants, microorganisms and marine organisms. They are characterized by exceptional structural variety and biological action. Due to the subtle change of natural conditions in varied natural means they tend to have complex molecular structures and functional groups which react selectively to biological targets. This is their property that has been used as a property to discover drugs to treat many diseases including infections, cancer, and inflammatory diseases. An important percentage of drugs that are presently approved are either natural products or compounds based on the natural molecular structure. The compounds are also sources of novel chemical scaffolds that can be used in the development of new therapeutic agents. Analogues are attributed to the natural products by researcher s to confer them with better pharmacological characteristics, increased stability, or reduced toxicity. Catalytic methods have gained significance especially in enabling such structural rearrangements in which chemists can produce new derivatives with effectiveness whilst maintaining the biological functionality of the original molecules[1].

Although it is essential, there are a number of practical issues with getting natural products with the help of natural sources. Lots of bioactive compounds are found in very low concentrations in their producing organisms. This makes the process of isolating enough quantities to carry out research or pharmaceutical production, challenging and expensive. Moreover, massive exploitation of biological resources can lead to environmental harm and endanger the sustainability of the ecosystem. The other weakness is that it is complex to isolate and purify natural compounds in mixtures found in the biological entities. Plant or micro-organism extracts usually contain a large number of components that need sizeable purification processes. These procedures are not efficient and usually time-wasting. Moreover, natural products are often too complicated to isolate and characterize due to their structural complexity. Due to such constraints, synthetic chemistry has opened the flood gates among scientists who can synthesize natural product analogues to mimic the biological activity of naturally occurring molecules[2] .

Synthetic chemistry offers potent means to make complex molecules that are inspired by natural products. Through these well thought out chemical reactions, scientists are able to recreate natural product structures or make altered derivatives with better pharmacological properties. Natural product analogues are of special use since this kind of product is used to explore the structure-activity relationship in a systematic way so that scientists can comprehend the effects of certain molecular characteristics on the biological activity. The development of catalytic synthetic techniques has allowed more and more intricate molecular structures to be built. More specifically, first-row transition metal catalytic reactions have found interest because they are

*Author for Correspondence:Jagjeet Singh

efficient and cost-effective in organic synthesis[2]. Also enzymatic methods have been combined with chemical methods and the method developed known as chemoenzymatic synthesis that combines the high selectivity of enzymes with the versatile nature of the chemical transformations to give a variety of natural product derivatives that are more efficient[3].

Catalysis has now become a major subject of contemporary synthetic chemistry since it enables chemical reactions to be more efficient and selective. Catalysts facilitate the reaction rate by reducing the activation energy needed for chemical changes and they do not change throughout the reaction. This is possible by allowing complex molecules to be produced with less steps, gentle reaction conditions and the use of less reagent. Catalytic transformations relating to oxidation, carbon-carbon bond formation, and hydrogenation are important in the synthesis and transformation of natural product backbones. These reactions enable to build complex molecular mechanisms and bring changes of structure that increase biological activity. Natural product scaffolds have also been isolated and directly modified using catalysts to allow them to be generated to produce superior therapeutic derivatives[1].

Heterogeneous catalysis is one of the various catalytic methods in organic synthesis that have received a lot of attention due to its simplicity of operation and environmental friendliness. Heterogenous catalysis is core of many industrial processes because of low cost, high conversion better selectivity, recyclability and minimal secondary pollutants[4]. In a heterogeneous catalytic system, the catalyst and the reactants are in different phases, the catalyst is commonly in the form of solid, and the reactants are in the form of either liquid or gas. The phase separation means that the catalyst is easily reused and recovered, and so heterogeneous catalysis is especially appealing to sustainable and industrial chemical reactions. The knowledge of the structure of catalytic active sites is one of the keys to increasing the efficiency of heterogeneous catalysts. It is the active sites that adsorb and transform the reactant molecules and the structural properties of catalyst plays a key role in the catalytic performance[5]. The improvements in catalyst design have allowed using materials with highly controlled surface structures that have enabled the researchers to increase the selectivity and efficiency of catalysts[6]. The recent advances in material science have also given a way to the single-metal-site catalysts, which are a blend of both homogeneous and heterogeneous systems. These catalysts are based on individual metal atoms on solid surfaces, and deliver defined active centres with the stability and recyclability characteristic of heterogeneous catalysts[7]. Furthermore, new catalytic substances like polymeric carbon nitride have also been considered as metal-free catalysts that can be used to carry out photocatalytic reactions and environmentally friendly chemical reactions[8]. The use of heterogeneous catalysis has been also studied to be applicable in environmental concerns, especially in the measures to be taken towards the use of carbon dioxide and the mitigation of emissions[9]. To illustrate, the carbon dioxide can be transformed into useful chemical substances through catalytic hydrogenation, which proves the prospect of heterogeneous catalysis in the area of sustainable chemical production[10]. These developments help to emphasize the relevance of heterogeneous catalytic technologies not only to modern synthesis but also to environmentally responsible chemistry[11]. Catalytic strategies, advances in catalyst design and the maturing heterogeneous catalytic systems that promote effective chemical transformations. The focus of these strategies is to evolve sustainable catalytic methods to be used to enhance the production of biologically active compounds.

Heterogeneous catalysis is a cornerstone in the contemporary chemical synthesis, facilitating effective conversion, by surface interaction reactions. In such systems, catalysts and reactants exist in other phases and reactions occurs on specific active sites of catalyst surface

(Fig. 1).

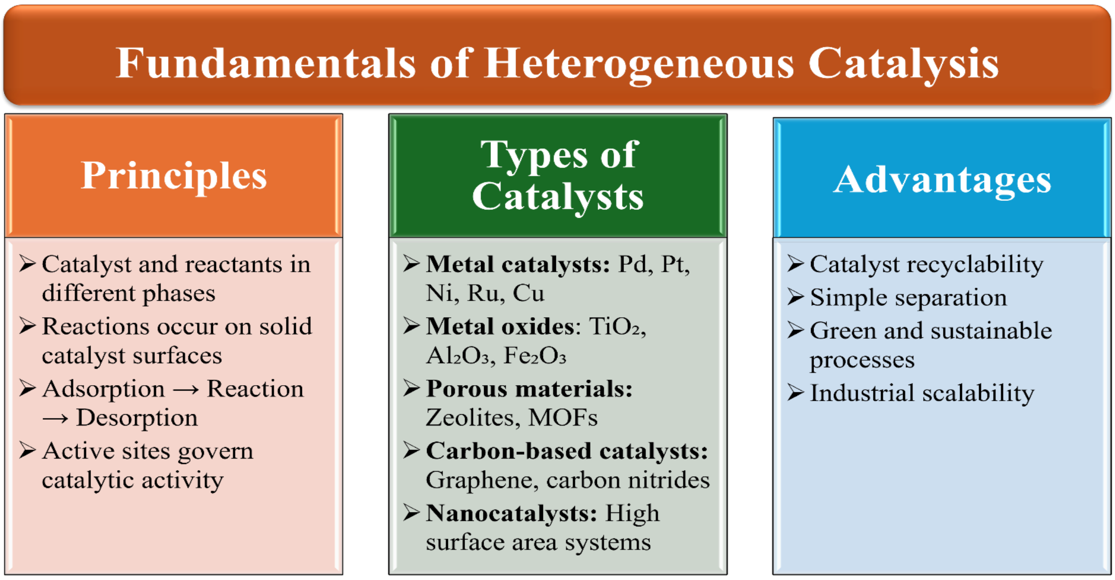

Figure 1. Fundamentals of heterogeneous catalysis

In heterogeneous catalysis, the reaction and the catalyst are in a different state, most usually a solid catalyst being used with liquid or gaseous reactants. The catalyst surface is the location where reactions take place; thus, the reactant molecules adsorb, this reaction takes place, and the product are desorbed. The catalyst-substrate interactions are important and the presence of active surface positions that allow the formation or breaking of bonds have a strong dependence on the efficiency of these processes. This knowledge of such surface interactions can be used to enhance the catalytic activity/selectivity in organic reactions. Homogeneous and heterogeneous catalytic pathways have been also used to help demonstrate reaction mechanisms as well as optimize catalytic activity in reduction reactions and other transformations[12]. Moreover, photochemical transformations like direct C-H functionalization with carbon dioxide can be catalyzed by surface-mediated activation, which demonstrates the wide range of reactions catalyzed by surfaces in making chemical reactions sustainable[13].

Heterogeneous catalysts are categorized according to their composition and structure properties. The supported metal catalysts are used commonly due to their capability of promoting the reaction involving hydrogenation, oxidation and making of carbon-carbon bonds, including palladium, platinum, nickel, ruthenium and copper. Metal oxide catalysts are also significant in the heterogeneous catalysis because of their thermal stability, redox, and acid-base reactions. Porous catalytic materials (zeolites and other engineered structures) offer high surface areas and crystallized channels which increases catalytic activity[14]. Another promising type of catalysts is metal-organic frameworks, the structures of which can be successfully tuned to optimize catalytic activity in oxidation, as well as other processes associated with it[15]. Also, carbon-based materials and nanostructured catalysts have been of interest due to their stability, high surface area, as well as capacity to host active catalytic species.

Heterogeneous catalysis has a number of strengths that render it especially appealing to the laboratory and industrial synthesis of chemicals. Recyclability of catalysts is one of the most vital advantages as the catalyst can be simply segregated out of the reaction mixture and reused. Such a property lowers the cost of operation and enhances sustainability of the process. The second benefit is that the product separation is very easy since the solid catalyst may be separated without the use of complicated purification processes. Environmentally friendly synthetic strategies are also supported by heterogeneous catalytic systems because they reduce the waste and facilitate a green reaction state[16]. Additionally, heterogeneous catalysts are very practical in industry as they have a high level of durability and scalability, so they are applicable in the formation of complex organic molecules and derivatives of natural products[17].

The natural products have played a significant role in the discovery and development of biologically active compounds. They are worth using in research on pharmaceuticals and chemicals because of their structural diversity and complexity in functions. A number of works have been known to emphasize the importance of catalytic strategies and synthetic approaches in reaching natural product structures and producing analogues associated with these structures. Table 1 displays the studies that were chosen to summarize the key literature contributions to the field of natural product research and analogue development.

Table 1. Catalytic strategies relevant to natural product and analogue synthesis

Catalytic system / approach	Reaction or application	Supporting Studies

Heterogeneous catalysts under microwave irradiation	Multicomponent reactions enabling rapid synthesis of complex organic scaffolds	[18]
Phosphine-functionalized metal–organic framework catalysts	Bridging homogeneous and heterogeneous catalysis for selective transformations	[19]
Surface organometallic heterogeneous catalytic systems	Active-site engineering for efficient organic synthesis	[20]
Engineered catalytic solvation environments	Biomass conversion into valuable chemical intermediates	[21]

These studies summarized highlight how advances in catalyst design and reaction engineering contribute to the efficient synthesis and modification of natural product frameworks.

Natural products are also a significant source of core to discover biologically active molecules applicable in medicine and biotechnology. Plant, microorganisms and marine compounds have distinct structural frameworks that tend to exhibit pronounced pharmacological activities. Natural products or molecules based on natural structures are used as many therapeutic agents such as anticancer drugs, antibiotics and anti-inflammatory compounds. The stereochemical diversity and chemical complexity of these molecules allow them to react specifically with their biological targets, and hence they are useful starting points in pharmaceutical research. The recent advances in catalytic chemistry and materials science have enabled the improvement of the ability to use natural product frameworks in chemical synthesis. Efficiency and selectivity of transformations of biomass-based or natural product-related molecules can be enhanced using catalytic systems that can generate controlled reaction environments[21]. Besides, the progress of the surface organometallic chemistry has shed light on the possibility of having complex molecular transformations through catalytic surfaces, helping to derive novel catalytic strategies to produce biologically relevant compounds[20].

Natural product analogues are synthetic variations of these motifs which are developed by altering the structural aspects of natural compounds but still have the core biological properties. The significance of these modified molecules on medicinal chemistry is that these molecules enable researchers to enhance the pharmacology of the natural compounds. Biological activity, stability and selectivity can be improved by structural changes like addition of new functional groups, change in stereochemistry or simplification of molecular structures. The importance of modern synthetic strategies lies in the production of a variety of natural product analogues. Such methods as multicomponent reactions offer efficient methods of forming complex molecules in one step and enable quicker investigation of the structural variety in analogue development[18]. Also, novel catalyst systems, including phosphine-functionalized metal-organic catalysts have been created to integrate the benefits of both homogeneous and heterogeneous catalysis and provide better control over catalytic reactions in analogue synthesis[19].

Synthesis of natural product analogues often involves catalytic reactions, which allow the easy functional group editing and assembly of elaborate molecular templates. A number of catalytic methods are widely used in organic synthesis such as hydrogenation and reduction reactions, oxidation reactions, formation of carbon-carbon bonds and multicomponent reactions. These catalytic methods offer general methods of altering natural product scaffoldings and produce a wide range of analogue structures. Figure 2 summarizes the key catalytic strategies that are employed in the natural product analogue manufacturing.

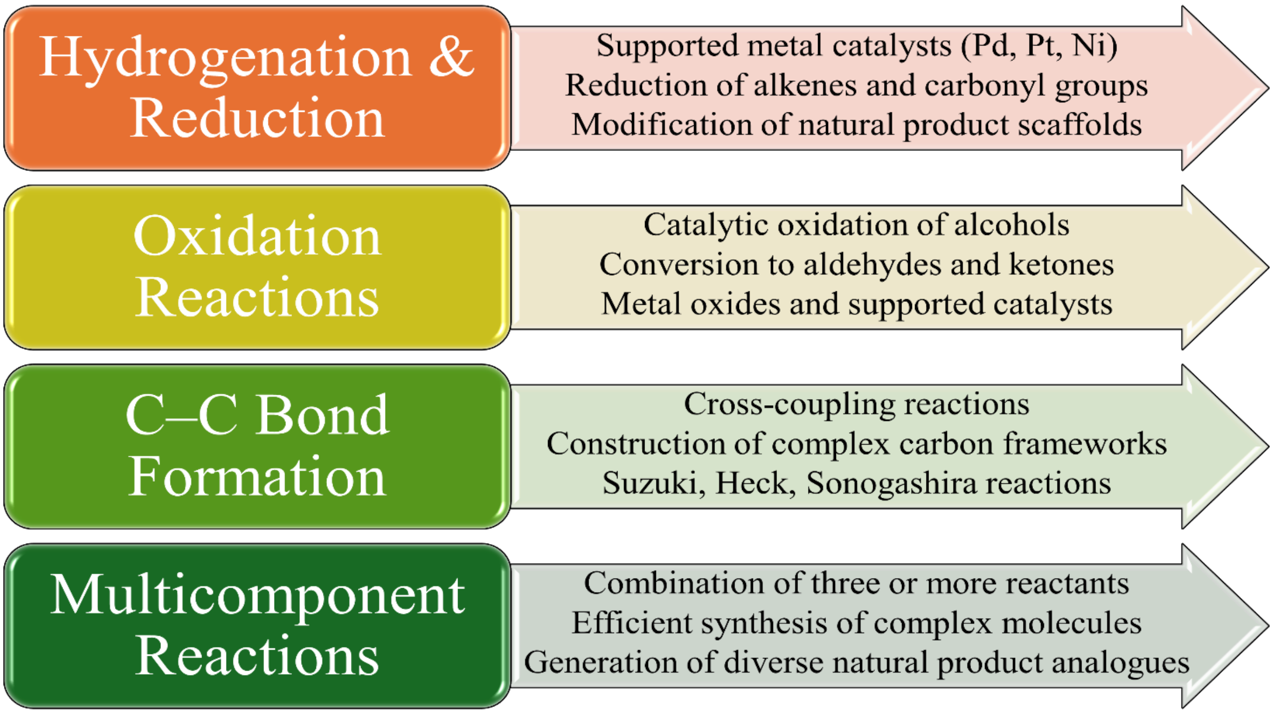

Figure 2.

These catalytic approaches enable selective functionalization of complex molecules and facilitate the construction of diverse chemical frameworks, thereby expanding the potential of heterogeneous catalysis in natural product analogue synthesis.

Reduction and hydrogenation reactions are vital in transforming natural structure of products and their derivatives. The transformations are generally conducted with the help of supported metal catalysts like palladium, platinum or nickel that are deposited on solids. Highly dispersed metal sites are available and therefore enable efficient activation of hydrogen molecules and selective reduction of functional groups such as carbon-carbon double bonds, carbonyls and nitro functionalities. The development of a range of heterogeneous catalysts, including isolated metal atoms, nanoclusters, and nanoparticles, has greatly contributed to the increase in catalyst performance and selectivity in hydrogenation reactions[22]. These catalytic systems have found extensive use in structural modification of natural product scaffolds where chemists were able to produce derivatives with enhanced stability and biological activity. The use of catalytic hydrogenation is now one of the crucial methods of converting complex molecules in the development of analogues.

Another strategy that is significant in the synthesis and functional modification of natural product analogues is Catalytic oxidation reactions. The reactions allow changing alcohols, hydrocarbons and other functional groups to more active intermediates that may then be further converted to biologically relevant compounds. The most common are metal oxide and supported catalysts which can offer stable catalytic surfaces that can be used in selective oxidation under controlled conditions. One of the most common applications of catalytic oxidation is in the alteration of bio-molecules and intricate organic substances to provide access to structurally diverse molecules applicable to pharmaceutical development[23]. Moreover, the nanostructured heterogeneous catalysts recently have received interest regarding their large surface area and enhanced catalytic activity, which allows selective reactions in a complicated molecular system[24].

Formation of carbon-carbon bond is a basic process in the formation of complex molecular structures in natural products. Reactions involving cross-coupling reactions and corresponding catalytic reactions can be used to form new carbon structures out of simple building blocks. These transformations have also become associated with the use of heterogeneous catalysts that offer greater stability, recyclability and operational simplicity in contrast to systems involving homogeneous catalysts. New trends in the catalytic materials have facilitated effective coupling reactions producing intricate organic structures at environmentally friendly conditions. As an example, engineered nanomaterial-based heterogeneous catalysts have been utilized to catalyze both A^3 and KA^2 coupling reactions, showing that they can be used to build carbon-carbon bonds in diverse steps in synthetic procedures[25].

Multicomponent reactions have become influential synthetic methods to produce complicated molecules within one reaction process. These reactions can be described as simultaneous combination of three or more starting materials in order to combine to produce structurally complex products in a highly efficient manner. Heterogeneous catalysts in these processes are beneficial in increasing the selectivity of the reactions, ease in purification of the products, and recyclability of the catalysts. Biginelli analogues and other heterocyclic frameworks have been productively prepared by green catalytic methodologies by use of inorganic heterogeneous catalysts[26]. Moreover, more recent technologies in reaction, like flow chemistry, have only enhanced the efficiency of multistep synthetic processes in the synthesis of natural products through continuous and controlled catalytic conversions[27].

The current breakthroughs in the development of catalysts have seen the creation of a number of novel catalytic frameworks that enhance the efficiency, selectivity and sustainability of reactions. Such novel catalytic systems now offer new possibilities to achieve complex chemical transformations in the field of organic synthesis and natural product analogue synthesis. A summary of the representative catalytic systems and applications in Table 2.

Table 2. Emerging catalytic systems and their applications in organic synthesis

Catalytic System	Key Characteristics	Applications in Organic / Natural Product Synthesis	Supporting Studies
Single-atom catalysts	Isolated metal atoms dispersed on solid supports with well-defined active sites	Highly selective hydrogenation, oxidation, and cross-coupling reactions	[28]
Metal–organic framework (MOF) catalysts	Porous crystalline materials with tunable metal nodes and organic linkers	Selective catalytic transformations and scaffold construction	[29]
Nanostructured catalysts	Metal nanoparticles and supported nanomaterials with high surface area	Efficient formation of heterocycles and complex organic frameworks	[30]
Photocatalysis and electrocatalysis	Light- or electricity-driven catalytic reactions enabling mild reaction conditions	Sustainable synthesis pathways and environmentally friendly transformations	[31]
Biosynthetic catalytic systems	Enzyme-mediated catalytic reactions in biological pathways	Formation of complex bonds in natural product biosynthesis	[32]

Table 2 Recent developments in catalyst design, complex molecule synthesis.

Single-atom catalysts (SACs) constitute a new type of catalytic material where individual atoms of metals are dispersed on solid surfaces. This atomic dispersion can maximize the use of metals and offer well-defined active sites which can improve catalytic activities. The isolated atoms are also controlled so that the reaction pathways can be clearly controlled and high selectivity due to the specific electronic and geometrical setting of the isolated atoms in contrast to the conventional nanoparticle catalysts. SACs have been shown to have good activity in various organic reactions such as hydrogenation, oxidation, and cross-coupling reactions. Their capacity to unite characteristics of both homogenous and heterogeneous catalysis is highly desirable especially in more sophisticated synthetic practice. The recent research emphasizes the recent increasing role of single-atom catalytic systems in organic reactions because they are highly efficient and can regulate their catalytic behavior[28].

Metal-organic frameworks (MOFs) are crystalline porous networks that are built using metal nodes and organic linkers. Due to their very structured structures, and adjustable pore environments, catalytic activity and selectivity can be tactfully controlled. Different metal centers and functional groups can be incorporated into MOFs because of their structural tunability, which results in the formation of reaction-specific catalytic sites. Such materials have received a lot of interest in their application in the organic synthesis, due to their large surface areas that allow the diffusion of a substrate and increase catalytic interactions. MOF-based catalysts can be used in natural product analogue synthesis to drive a specific transformation and to be utilized to construct complex molecular frameworks with selectivity. They can thus be used to design advanced catalytic systems in the field of synthetic chemistry due to their modular architecture[29].

Nanostructured catalysts (such as metal nanoparticles and supported nanomaterials) have gained a growing role in catalytic chemistry of the modern world. Their high surface-to-volume ratio enhances the availability of catalytic sites and in most cases, the catalytic efficiency is enhanced. Nano-particles are also capable of having distinct electronic characteristics which increase selectivity in their reactions and provide reactions that would otherwise not be easily realized using bulk catalyst. Nanostructured catalysts have been utilized in organic synthesis to support a large variety of reactions, including hydrogenation, oxidation and the formation of carbon-carbon bonds. Such catalytic systems are especially beneficial in the synthesis of complex heterocyclic structures that are natural products and bioactive molecules[30].

Photocatalysis and electrocatalysis have also become potent methods towards facilitating sustainable chemical reactions. Photocatalytic systems can use light energy to energize catalysts to catalyze chemical reactions and electrocatalytic processes can use electrical energy to catalyze redox reactions. These procedures allow reactions to be run in milder conditions, and do not require the use of hazardous reagents. Photocatalysis and electrocatalysis in photocatalysis and electrocatalysis are discussed during recent years as the pathways of green synthesis, especially in the synthesis of biologically relevant molecules. Other forms of environmentally friendly approaches to chemical synthesis have been inspired by biological catalytic systems (such as microorganism-mediated transformations), and these biologically inspired systems are also capable of transforming target molecules[31]. Also, the examination of biosynthetic pathways shows how catalytic reactions would facilitate the establishment of complex connections in the structure of natural products, and this information can be useful in creating new catalytic strategies[32].

Green catalytic approach is becoming an important part of the contemporary chemical synthesis as it lowers environmental implication and does not lead to low reaction rate. Other methods that have been applied in leading towards sustainable synthesis include solvent-free reactions, microwave-assisted catalysis, flow chemistry, and biomass-derived catalysts. The most important green catalytic approaches and their environmental advantages are presented in Figure 3.

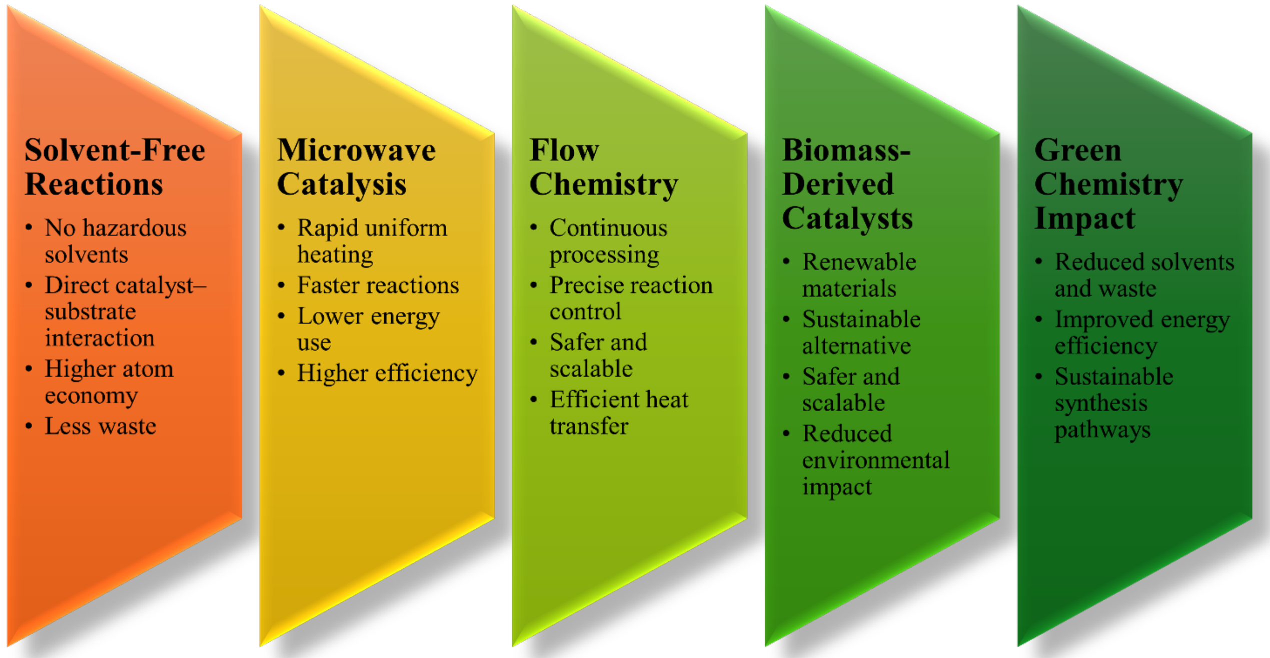

Figure 3. Green and sustainable catalytic approaches

These approaches promote environmentally responsible chemical processes by minimizing solvent use, reducing waste generation, improving energy efficiency, and enabling sustainable synthesis of natural product analogues.

The application of solvent-free reactions in the context of green chemistry has received a consistent interest due to the fact that the reaction does not involve the use of dangerous organic solvents and also helps to minimize the amount of chemical waste. Such reactions are normally performed at solid-state or low solvent concentrations, in which reactants can react at the catalyst surface. These methods enhance atom economy, make purifying methods relatively simpler and have less environmental effects. Solvents are not used when at least one of the catalysts are in solid form and this is known as solvent-free in heterogeneous catalysis. As an illustration, mesoporous vanadium-doped titania nanoparticles have been utilized as heterogeneous catalysts of strength in solvent-free Hantzsch reactions in the synthesis of polyhydroquinoline derivatives. The reactions show that under solvent-free conditions, heterocyclic compounds potentially useful in the field of pharmaceutical chemistry can be synthesized efficiently[33].

The latest type of catalyst-based catalysis, which has not been pursued to its limits by the scientific community yet, is called microwave-assisted catalysis. A catalytic reaction assisted by microwaves is a significant process in the sustainable production of chemicals since the reaction rates and speed can be increased over traditional heating processes. A consistent distribution of energy is afforded by the use of microwave irradiation, a property that increases the rate of catalytic reactions and in many instances, the reaction yield and efficiency is enhanced. This has been very common in heterogeneous catalytic systems where catalysts absorb the microwave energy and enhance quicker chemical reactions. Catalytic reactions involving microwave power also decrease reactions times and energy required and are therefore appealing in environmentally friendly synthesis. Moreover, catalytic hydrogenation and associated transformations were reported with catalytic systems based on metals, which allow achieving facilitated reduction processes under mild conditions[34].

Flow chemistry is a new strategy of scalable and sustainable chemical synthesis. Continuous flow systems have the reactants flow through a reactor with the catalyst and parameters of the reaction like temperature, pressure and residence time can be controlled accurately. The technology enhances the safety of the reactions and increases the heat and mass transfer and scale-up of catalytic processes. Flow reactors are also advantageous especially in heterogeneous catalysis in that solid catalysts can be immobilized in the reactor and the production of target compounds can occur continuously. Also, the efficiency of heterogeneous catalysts in continuous flow systems has been enhanced by the development of new catalyst designs, such as surface organometallic chemistry[20].

Biomass-based catalysts are a greener substitute of conventional catalytic materials since they are made out of renewable resources like plant-based material, agricultural waste, or the bio-derived carbon source. The catalysts are usually functional groups or porous (like a catalytic site) that allows them to be useful in organic transformations. Coupling or functional group transformations reactions have been made using biomass-based catalytic materials as alternatives to metal catalysts. Recent reports have also shown that catalyzed cross-coupling reactions can be carried out in ligand-free conditions, which requires expensive and toxic additives, and still retain catalytic activity[35]. The evolution of solvent-free reactions, catalysis in the microwave environment, flow chemistry, and catalysts prepared with biomass, is an indication of the increased focus on sustainable chemical methods. All these methods decrease the amount of solvent used, decrease the amount of waste produced, and increase energy and catalytic efficiency. Consequently, green catalytic technologies are becoming more relevant to the synthesis of complex organic molecules, such as natural product analogues, and to provide environmentally responsible chemical synthesis.

To prepare natural product analogues, typically sophisticated catalytic methods are used to build complex molecular structures and provide functional modifications. Catalytic strategies employed in the preparation of various classes of natural product derivatives are summarized in Table 3.

Table 3. Catalytic strategies used in the synthesis of natural product analogues

Natural Product Class	**Catalytic Strategy**	**Key Transformation**	**Supporting Studies**
Alkaloid analogues	Pd-based heterogeneous catalysis	C–C bond formation using polymer-supported palladium catalysts	[36]
Flavonoid derivatives	Photocatalysis using carbon nitride catalysts	Photoredox functionalization of aromatic frameworks	[37]
Terpenoid analogues	Pd-based heterogeneous hydrogenation catalysts	Selective hydrogenation of unsaturated molecular frameworks	[38]
Heterocyclic natural product derivatives	MOF catalysts and olefin metathesis	Catalytic ring formation and C–C bond construction	[39], [40]

Alkaloids are a significant group of natural products, heterocyclic with nitrogen and may have crucial pharmacological effects. Synthesis of alkaloid analogues usually includes the use of catalytic methods that allow a selective bond formation and the change of functional groups. The heterogeneous catalytic systems have extensively been studied to enhance the efficiency of the reaction and stability of the catalyst in these transformations. One such example is the development of palladium catalysts immobilized in functionalized polymer matrices to promote the formation of carbon-carbon bonds which is one of the main steps in the formation of complex structures of alkaloids. These catalytic systems lead to a higher catalyst life and reaction selectivity to produce structurally varied alkaloid derivatives, which are useful in medicinal chemistry[36].

Flavonoids are natural products of polyphenols which are abundant in plants and which are antioxidants, anti-inflammatory and anticancer agents. Formation of flavonoid derivatives frequently necessitates a catalytic reaction which brings functional alteration on aromatic rings. Efficient ways of carrying out such transformations under mild conditions have been developed with Photocatalytic techniques. Several carbon nitride materials have been demonstrated to be heterogeneous photocatalysts in promoting photoredox reactions to allow selective functionalization of aromatic compounds. These catalytic systems operate to perform chemical reactions with the use of visible light, providing greener alternatives to the most common synthetic systems available to the chemical modification of flavonoid scaffolds[37].

Terpenoids are one of the biggest natural product classes and they have various biological activities. The terpenoid analogue synthesis is often catalytically transformed in order to allow the selective hydrogenation or structural rearrangement of unsaturated molecular frameworks. Recent developments on the design of heterogeneous catalysts have provided a better approach to control hydrogenation reactions through variations in catalyst surfaces and ligand environments. As an example, palladium based catalysts containing ligand type surface features have been shown to exhibit enhanced selectivity in hydrogenation reactions. These catalysts enable the active control of catalysis, which is especially required when working with complex terpenoid molecules that have several active functional groups[38].

The heterocycle structures are widely found in most natural products and pharmaceutical compounds. Synthesis of heterocyclic natural product analogues can be based on catalytic reaction that can create new ring systems and carbon-carbon bonds. The ability of metal-organic frameworks to perform such transformations has led to high-surface area and controllable pore environments via their development as promising heterogeneous catalysts. These materials have defined catalytic sites, which promote effective organic conversions, such as the construction of heterocyclic structures. Moreover, heterogeneous catalyst strategies have proven to be highly versatile in producing heterocyclic derivatives, with olefin metathesis being one of the most widely used catalytic methods in the synthesis of complex ring systems being used in natural product synthesis[39,40].

Although the heterogeneous catalytic systems have made a huge step forward in synthesizing natural product analogues, there are various challenges and limitations that still limit the general use of such catalytic systems. Catalyst deactivation is one of the greatest problems and may happen as a result of either catalyst poisoning, structure modification, or aggregation of active catalytic sites, during repeated reaction cycles. As a relevant issue of concern in heterogeneous catalysis, maintaining catalytic stability without deactivation is a challenge in catalytic systems that have high activity. The other problem is the selectivity of reactions in the context of complex substrates, mostly containing more than one reactive functional group which can be subjected to competing reactions. Moreover, the preparation of catalysts, particularly of advanced materials (such as engineered metal-organic frameworks and supported metal catalysts), can be expensive, which can limit their large-scale implementation[41]. Scalability is also an issue in industrial application where conditions used in reactions at the laboratory level might not be directly applicable in large scale processes. In addition, most catalytic systems have a low substrate scope, which can be utilized only in certain sets of molecules. Addressing these shortcomings is crucial to the diversification of the general usefulness of catalytic strategies in the manufacture of complex natural products and analogs[42].

Future directions of the use of heterogeneous catalysis in synthesis of natural product analogues are probably to include the adoption of opportunities provided by computational catalysis and data analysis to understand reaction mechanisms and catalyst behaviour better. The artificial intelligence (AI) and machine learning will be used to predict the catalyst structures, the reaction outcomes, and thus perform catalyst discovery and optimization much faster. The other area of concern will be the design of extremely selective catalysts that can conduct intricate transformations in a more efficient and less by-product manner. Furthermore, there will be continuous development in translating catalytic innovations to industrial processes with a focus on scalable, cost-effective, and environmentally sustainable catalytic processes.

Heterogeneous catalysis has become an effective and flexible tool of synthesis of natural product analogues, and provides a great benefit in terms of efficiency, selectivity, and sustainability. It is making its role pivotal in building and elaborating the structure of natural products. New catalytic materials, such as single-atom catalysts, metal-organic frameworks, and photocatalytic systems, have also increased the performance of catalysts and provided new possibilities in selective synthesis. Furthermore, solvent-free reactions, microwave-assisted catalysis, flow chemistry, biomass-based catalysts, and other environmentally friendly methods of reducing green chemistry can be applied to making chemical processes environmentally responsible. Although these improvements have been made, the problems of catalyst deactivation, selectivity, and scalability continue to be significant issues of current study. The continued development of this area in the future is likely to be based on the combination of computational modeling, artificial intelligence, and advanced materials science, to develop more efficient catalytic systems. Further development of heterogeneous catalysis will thus be important in making it possible to discover the sustainable and scalable synthesis of biologically relevant natural product analogues to practical uses.

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