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Hydroxychavicol from *Piper beetle Linn.*: A Comprehensive Narrative Review of Its Chemistry, Pharmacological Activities, Molecular Mechanisms, Therapeutic Potential, and Future Perspectives

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Abstract: Hydroxychavicol (4-allylbenzene-1,2-diol) is the main phenolic bioactive compound found in *Piper betle Linn.*, an herbal plant widely used in traditional medicine across Asia. In the last two decades, hydroxychavicol has gained a lot of attention from researchers because of its diverse range of pharmacological properties and potential as a multi-purpose therapeutic substance. This narrative review aims to elaborate on the existing understanding of hydroxychavicol's chemistry, natural presence, isolation, pharmacological characteristics, molecular mechanisms, drug delivery systems, therapeutic potential and future possibilities. An exhaustive search was conducted for the literature, focusing on peer-reviewed journals covered in PubMed, Scopus, Web of Science, Science Direct, and Google Scholar, primarily from the years 2000 to 2026. Experimental results indicate that Hydroxychavicol has important antioxidant, antimicrobial, anti-inflammatory, anti-cancer, anti-diabetic, wound healing, liver protecting, heart protecting, brain protecting, and immune disease preventing properties. The drug operates through the changes in different cellular pathways like NF- κ B, Nrf2, PI3K/Akt, MAPK, and mitochondrial pathways affecting the processes of oxidative stress, inflammation, and apoptosis. Though the drug seems to be very effective, it is not widely used in practice because it does not dissolve well in water, has poor absorption and is destroyed by our body very quickly. New technology developments such as nanoparticles, liposomes, solid lipid nanoparticles and gels allow overcoming existing pharmaceutical problems related to the drug so that its efficiency in treatment can be increased. The evidence in totality points towards the important presence of a multitarget phytochemical called hydroxychavicol which shows great promise to be utilized in the prevention and management of chronic inflammatory diseases, infectious diseases, metabolic disorders, and cancer. However, there is a need for pharmacokinetic research, formulation standardization, and clinical trials on a bigger scale.

Keywords: Hydroxychavicol; *Piper betle Linn.*; phytochemicals;

pharmacological activities; mechanism of action; antioxidant; anticancer; drug administration; potential of the treatment.

INTRODUCTION:

Medicinal plants have been among the most trusted sources of pharmacological agents from the beginning of time till date. Due to the enormous phytochemical variety found within medicinal plants, there have been remarkable contributions made in terms of discovery of drugs which either acted as therapeutic agents directly or as a source for semi-synthesis and synthesis of various pharmaceuticals. According to the World Health Organization (WHO), up to 80% of the world's population relies on traditional herbal medicines for their health care needs especially in the developing countries. Increased prevalence of chronic conditions, antimicrobial resistance, metabolic syndromes and cancers in conjunction with drawbacks of some of the synthetically prepared drugs has led to renewed interest in medicinal plants due to their safer and efficacious therapeutic potential.

Natural products have historically served as the cornerstone of pharmaceutical innovation because of their unparalleled structural diversity and broad spectrum of biological activities. Numerous plant-derived compounds exhibit antioxidant, antimicrobial, antiviral, antifungal, anti-inflammatory, antidiabetic, immunomodulatory, cardio protective, neuroprotective, and anticancer properties, making them promising candidates for the prevention and treatment of both communicable and non-communicable diseases. Unlike many conventional synthetic drugs that primarily target a single molecular pathway, phytochemicals frequently exert multitarget pharmacological effects by modulating oxidative stress, inflammatory mediators, apoptosis, immune responses, microbial virulence, and intracellular signalling pathways. Such pleiotropic mechanisms are particularly advantageous for the management of multifactorial diseases, where simultaneous regulation of multiple biological processes may improve therapeutic efficacy while reducing the likelihood of drug resistance and adverse effects.

With recent advancements in the fields of phytochemistry, analytical chemistry, metabolomics, molecular pharmacology, and computational drug design, there has been a great improvement in the identification, isolation, and analysis of Phyto constitutions with biological activities in medicinal plants. All these advancements have helped in gaining more knowledge about the chemical composition, pharmacology, and effectiveness of phytoconstituents from medicinal plants. Hence, medicinal plants play a vital role in the discovery of new lead molecules to meet the increasing demands for safer and effective therapeutic drugs.

Of the large variety of medicinal plants studied all around the world, one of the plants which has become a prominent medicinal plant owing to its vast ethno pharmacology and amazing pharmacological properties is *Piper betle* Linn., family: Piperaceae, commonly called betel vine. *Piper betle* is cultivated extensively in South and Southeast Asia, including countries like India, Sri Lanka, Bangladesh, Nepal, Thailand, Malaysia, Indonesia, and Vietnam, where it has been employed for hundreds of years in traditional systems of medicine such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine. Apart from being culturally and economically significant, *Piper beetle* has also been traditionally used in the treatment of oral ailments, respiratory ailments, gastrointestinal problems, wounds, burns, skin infections, inflammations, and metabolic disorders. Phytochemical and pharmacological studies conducted on the plant have confirmed many of these traditional uses, and thus, *Piper beetle* has proved to be an important medicinal plant with great pharmaceutical and biomedical significance.

Piper beetle Linn. has been widely employed in folk medicine for ages due to its wide range of medical uses. Betel leaves were traditionally recommended in Ayurveda, Siddha, Unani, and Traditional Chinese Medicine for the treatment of infections of the mouth, bad breath, cough, bronchitis, asthma, dyspepsia, constipation, wounds, burns, skin conditions, rheumatism, inflammation, and diabetes. Leaves in fresh form have been traditionally used as antiseptics, carminatives, digestive stimulants, expectorants, pain relievers, antioxidants, and agents to heal wounds, whereas leaf extracts have been used for the treatment of microbial infections and inflammations. Widespread traditional uses of *Piper beetle* have led to many pharmacological studies that have confirmed the traditional medical claims through experimental and preclinical research [2,5,7,9].

The Botanical Profile of *Piper beetle* Linn:

Taxonomy:

Piper beetle Linn. is found in the family of Piperaceae and it is one of the largest families of flowering plants which consists of about 3,600 species of plants mainly found in tropical and subtropical countries. The genus Piper consists of about 1,000–2,000 species and a significant number of those organisms have medicinal, economic and aromatic value.

The taxonomy of *Piper beetle* is as follows:



- **Kingdom:** Plantae
- **Division:** Magnoliophyta
- **Class:** Magnoliopsida
- **Order:** Piperales
- **Family:** Piperaceae
- **Genus:** Piper
- **Species:** Piper beetle Linn

BOTANICAL DESCRIPTION OF *PIPER BETLE*:

The botanical description suggests that Piper beetle is a fast-growing, climbing vine in tropical Asia. It is a perennial plant that depends on external supports in climbing and growing, as it has healthy and long branches that emanate from its nodes [2,4]. The stem of the plant is sometimes thick at the nodes and cylindrical in shape which allows good propagation of this vine in favourable conditions [3,14]. The leaves are by far the most important parts of the plant with regard to their economic and medicinal values. They are heart-shaped (cordate), simple, glabrous, and smooth-surfaced. These leaves have a characteristic aromatic odour due to the presence of volatile essential oils. They have reticulate venation with prominent lateral veins starting at the base of the leaf [2,3]. Different cultivars of Piper beetle display variations in leaf size, colour, flavour, and chemical composition.

As dioecious plants, this species produces male flowers on separate plants from those that bear female flowers. They have small flowers that do not have a perianth and that grow inflorescent in spikes. Flowering is rare in cultivated material as the material is often propagated vegetatively and this results in a reduced likelihood of achieving any fruit production. The root system of the plant comprises roots found both in the ground and aerial or adventitious roots that grow from the stem. The aerial roots enable the plant to cling to various structures and improve its ability to take up water and nutrients thus supporting the rapid growth of the vine in moist climatic conditions [3,14]

Geographical Distribution:

Piper beetle is widely distributed all over Asia and is believed to have emanated from the Malaysian region where it spread to neighbouring countries as a result of cultivation and trade [2,4]. The plant is widely cultivated in India, Sri Lanka, Bangladesh, Nepal, Myanmar, Thailand, Malaysia, Indonesia, Vietnam and other tropical countries due to its medicinal, cultural and economic importance [2,8].

India has been recognized as one of the leading producers of betel leaves with extensive cultivation in the states of Tamil Nadu, West Bengal, Odisha, Karnataka, Andhra Pradesh, Kerala, Assam and Bihar. The plant thrives and grows well when the climatic conditions are warm and humid and when there is rich well-drained soil with sufficient quantity of organic material present. Maximal growth of the plant is observed when the temperature is between 20 and 35 degrees Celsius [4,14].

Cultivation and Propagation:

Piper beetle is commonly cultivated commercially through vegetative propagation by means of stem cuttings that are healthy and have three to five nodes [14]. Fertile loamy soil is necessary, along with considerable atmospheric humidity, sufficient irrigation, and some shade for optimal growth of the crop. Continuous practices of pruning, nutrient management, and disease prevention are fundamental to improve the quality of leaves and maximize production [2,14]. Since flowering and seed formation occurs rarely in cultivation conditions, vegetative propagation guarantees the maintenance of genetic uniformity and essential agronomy features in cultivated strains [3].

Phytochemical content of betel leaves depends on various parameters, such as type of cultivar, location, and climate, as well as soil properties and growing techniques used. The differences in the above factors effects variations in the concentrations of main compounds, such as hydroxychavicol, chavicol, chavibetol, and eugenol, which, in turn, leads to the differences in medicinal characteristics of the plant. [2,15].

ETHNOBOTANICAL IMPORTANCE AND TRADITIONAL MEDICINAL USES:

The use of Piper beetle Linn. in cultural and traditional medical practices of several Asian countries has been around for centuries [9,10]. Betel leaves are used in traditional culture in various ceremonies such as in religious events, weddings, and social affairs for hospitality, wealth, and health. Betel leaves are also widely used in traditional medicinal practices such as Ayurveda, Siddha, Unani, Traditional Chinese Medicine, and other related local healing practices for curing various diseases [9,11]. Through traditional consumption methods, the fresh leaves can be consumed as is or as decoctions, infusions, poultices, or extracts in cases of oral diseases, halitosis, dental caries, coughs, bronchitis, asthma, digestion issues, constipation, wound infection, skin infections, rheumatism, headaches, etc. [10-12]

Because of their extensive history in terms of antiseptic and antimicrobial properties, betel leaves are often crushed and applied directly on wounds or skin in order to aid in healing [11,13]. Besides, heated leaves are traditionally used to alleviate cough or other respiratory diseases, and the juice is administered in cases of earaches and problems relating to indigestion [9,10]. The medicinal benefits of Piper beetle can be largely attributed to its vast composition of phytochemicals, especially phenolic compounds and essential oils that are well known to have many different properties such as antioxidant, antimicrobial, anti-inflammatory, analgesic, and immunomodulatory activities [10,12,14]. The studies conducted for validating the claims of the traditional uses of this plant have also confirmed that it possesses many important activities such as antibacterial, antifungal, antiviral, antidiabetic, gastroprotective, hepatoprotective, anti-wound healing, and anticancer activities in both in vitro and in vivo studies [11–15]. Henceforth, these results give strong scientific validation to the medicinal use claims made for *Piper beetle*, and help in identifying the biodynamic phytochemicals that can be used for drug development. Not only the medicinal properties, *Piper beetle* has economic significance as well because of its extensive usage and cultivation in the food and pharmaceutical industries [10,14]. The interest in this plant has promoted the research to isolate and characterize the different phytochemicals, especially hydroxychavicol due to its potential in the development of new herbal remedies and advanced drug delivery systems [14,15].

The Phytochemistry of *Piper beetle* and Hydroxychavicol

Phytochemical Properties of *Piper beetle*

The most significant pharmacological benefits of Piper beetle must be due to its chemically varied phytoconstituents. In-depth phytochemical studies proved that betel leaves have an abundance of phenolic compounds, flavonoids, phenylpropanoids, alkaloids, terpenoids, saponins, tannins, glycosides, steroids,

and volatile essential oils [17,18]. All the above said phytochemicals together help the plant with its oxidation resistance, anti-bacterial, anti-inflammatory, anti-cancer, healing, and immune properties. Among those phytoconstituents, it's the phenolic compounds that are crucial as the biggest source of medicinal properties of Piper beetle. As per research papers, Hydroxychavicol, chavicol, chavibetol, eugenol, allyl pyrocatechol, safrole, and methyl eugenol are mentioned to be the most important phenolic ingredients in betel leaves. The amount of accumulation of these compounds is dependent on the variety of the plant, regions it grows in, climate, time of harvesting the leaves, and methods of extraction of the phytochemicals [18,21].

In addition to the presence of several phenolic components in Piper beetle, it contains a good amount of flavonoids like quercetin and catching along with terpenoids, phytosterols, sugars, amino acids, vitamins, and minerals, which altogether increase its effectiveness. The volatile essential oil component, creating the characteristic smell of betel leaves, is made mainly of phenylpropanoids and terpenes that possess high antimicrobial and antioxidant properties. The invention of modern technologies, such as the use of gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LC-MS), nuclear magnetic resonance (NMR), and Direct Analysis in Real Time Mass Spectrometry (DART-MS), has contributed greatly to the investigation of phytochemicals of Piper beetle. These methods have allowed for a certain confirmation of the presence of bioactive substances in Piper beetle. Among all phytochemicals identified in Piper beetle, hydroxychavicol has gained the greatest scientific attention due to its richness in betel leaves and wide spectrum of medicinal properties. Hydroxychavicol is proven to be an important element in biological properties of Piper beetle as a future drug and as a possible delivery system.

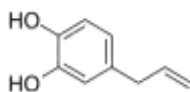
Hydroxychavicol: Chemistry, Structure and Physicochemical Properties

Hydroxychavicol (4-allylbenzene-1,2-diol), also called 4-allylpyrocatechol, is one of the main phenolic substances obtained from the leaves of Piper beetle Linn. It is considered as the main active compound responsible for the pharmacological activities of this plant [25,26]. It forms a group called phenylpropanoids and has received a lot of attention due to its various biological activities and therapeutic potential [27]. From a chemical point of view, hydroxychavicol is made of a benzene ring with two hydroxyl groups at ortho position and an allylic chain which gives both hydrophilic and lipophilic properties to hydroxychavicol [25].

The two adjacent hydroxyl groups boost the efficiency of hydroxychavicol in terms of the capacity for hydrogen transfer and radical scavenging [28]. Another important property of hydroxychavicol is the allylic moiety which allows this compound to act on biological membranes and targets [27].

Hydroxychavicol is designated as $C_9H_{10}O_2$ and weighs about 150.17 g/mol. It has a pale yellow to light brown oily appearance with low water solubility but good solubility in organic solvents such as ethanol, methanol, acetone, and ethyl acetate. As a result of its physical and chemical features, hydroxychavicol influences its absorption, stability, and pharmaceutical formulations. Studies have shown that hydroxychavicol is vulnerable to oxidation on exposure to air, heat, and light because of the catechol functional group. Oxidative breakdown of hydroxychavicol can affect its chemical stability and biopharmaceutical efficacy. As a result, it is necessary to utilize suitable methods of extraction, storage, and formulation in order to prolong its stability and effectiveness.

Due to its chemical structure, hydroxychavicol is able to interact with various molecular targets connected to oxidative stress, inflammation, apoptosis, bacteria growth, and cell reproduction. For these reasons, hydroxychavicol should be considered a guiding molecule for further research and development of drugs with antioxidant, anti-microbial, anti-cancer, and anti-inflammatory properties.



Hydroxychavicol Biosynthesis:

The biosynthesis of hydroxychavicol takes place in the plant Piper beetle through the phenylpropanoid metabolic pathway, which is regarded as one of the main secondary metabolic pathways in higher plants of

these species. At first, the biosynthesis of hydroxychavicol starts with L-phenylalanine amino acid, which is transformed to trans-cinnamic acid by the enzyme phenylalanine ammonia-lyase (PAL). It is claimed that PAL is the rate-limiting enzyme in the process of phenylpropanoid biosynthesis, and after the enzymatic reactions involving hydroxylation, methylation, and side-chain modifications, the individual phenylpropanoids, for example, hydroxychavicol or some other phenolic compounds in the Piper beetle plant are formed.

The concentration of hydroxychavicol in betel leaves is dependent on several biological and environmental factors such as plant genotype, cultivar variety, leaf maturity, climate, soil composition, area of growth, time of harvesting, and post-harvest treatment. Hydroxychavicol is a key defence phytochemical that defends the plant from oxidative stress, microbial organisms, insect attack or other environmental threats.

Its production is elevated in response to either biotic or abiotic stresses which increases its ecological importance for plant survival and adaptation. The study of the biosynthetic pathway of hydroxychavicol has a great pharmaceutical potential because it allows the implementation of metabolic engineering, plant tissue culture or biotechnology to enhance its production.

3.4 Analysis of Hydroxychavicol

Connected with the effect of betel leaves on human health [31,39]. Lastly, liquid chromatography and mass spectrometry (LC and MS) has high specificity and sensitivity for detecting hydroxychavicol from complex plant matrices and, therefore, this type of analysis has become very popular among researchers in phytochemistry [40].

The identification of hydroxychavicol and the structural specifications are very important for maintaining the quality of Piper beetle-derived phytopharmaceuticals. Due to progress in analytical equipment, hydroxychavicol can be identified and quantified from both purified and crude plant extracts [37,38].

High-performance liquid chromatography (HPLC) is one of the best strategies of analysis of hydroxychavicol considering its high sensitivity and generalizability [37]. HPLC proved to be a working method for standardization of Piper beetle extracts and sorting the samples in terms of hydroxychavicol content through various extraction techniques [38]. Moreover, gas chromatography and mass spectrometry (GC and MS) is an important analytical tool which is used for identification of volatile and semi volatile phytochemicals from Piper beetle. The results of several studies using GC-MS confirmed the identification of hydroxychavicol as one of the most important phenolic compounds.

The structural confirmation of hydroxychavicol usually involves two significant analytical methods, nuclear magnetic resonance (NMR) spectroscopy and Fourier-transform infrared (FTIR) spectroscopy [36,41]. NMR supplies important information concerning the molecular structure and arrangement of protons, while FTIR helps to distinguish chemical functional groups, particularly the presence of phenolic hydroxyl groups and allyl group in hydroxychavicol [41]. The use of these two methods allows for accurate determination of the structure of hydroxychavicol and correct assessment of the quality of compounds.

Direct Analysis in Real-Time Mass Spectrometry (DART-MS) has become one of the fastest and most accurate analytical techniques for direct identification of Piper beetle phytochemicals without detailed sample preparation procedures [32]. This method contributes to the determination of hydroxychavicol and other bioactive substances of interest and is very useful for fingerprinting, verification of the identity of various plant materials, and assessment of the quality of herbal drugs [32]. The combination of chromatographic and spectroscopic methods gives sufficient data on the chemical nature, purity, and concentration of hydroxychavicol. These techniques are essential to the standardization of extracts from Piper beetle.

Pharmacokinetics Features and Pharmaceutical Problems of Hydroxychavicol

Due to its wide variety of biological activities, Hydroxychavicol has gained substantial attention as a fruitful plant-based product. Notwithstanding its strong pharmacological properties, multiple physicochemical and pharmacokinetic restrictions prevent hydroxychavicol from being successfully

applied in practice [42,43]. Like many other naturally occurring phenols, hydroxychavicol has a very low solubility in water and is prone to oxidative breakdown. This leaves hydroxychavicol unstable during storage and production [42].

When hydroxychavicol enters the body, it may be exposed to active metabolism, resulting in a decreased systemic exposure and a low level of bioavailability [43]. The degradation process can also be hastened by the environmental factors, such as certain temperature conditions, acid or alkaline environment, presence of oxygen, and exposure to light [44]. Thus, condition of implementation would imply pharmaceutical difficulties in the production process.

Pharmacological Effects of Hydroxychavicol

Antioxidant Effect

Oxidative stress is caused by the imbalance between the generation of reactive oxygen species (ROS) and the endogenous defence mechanisms against them, leading to occurrence of many chronic illnesses, including cancer, diabetes, heart diseases, and neurodegenerative diseases [48,49]. Therefore, intensive search for natural antioxidants is conducted.

Hydroxychavicol is one of the main constituents of Piper beetle and possesses very strong antioxidant properties owing to the catechol structure with two neighbouring hydroxyl groups attached to the aromatic ring [50]. Hydroxyl groups are able to transfer the hydrogen atoms (or electrons) to the reactive radicals and stop oxidative chain reactions [50,51]. Therefore, using hydroxychavicol it is possible to eliminate superoxide radicals, hydroxyl radicals, nitric oxide radicals, and some other reactive oxygen species produced by cells.

Antibacterial Effectiveness

Hydroxychavicol has gained significant recognition as an organic antibacterial substance due to its wide-ranging activity against both Gram-negative and Gram-positive bacteria [7,11]. The increasing incidence of multidrug-resistant bacteria has sparked interest in the exploration of plant-based antibacterial compounds with innovative ways of action. Among the active ingredients derived from the Piper beetle plant, hydroxychavicol shows substantial antibacterial effectiveness against important disease-causing microorganisms such as *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Klebsiella pneumoniae*, and *Bacillus subtilis* [7,36]. Research has shown that hydroxychavicol has several methods of antibacterial action.

It works by disrupting the integrity of the bacterial cell membrane, raising the permeability of the membrane, permitting the leakage of the intracellular content, and affecting the various processes happening inside the living cell, which eventually leads to bacteria death [36]. Hydroxychavicol in the cells of microorganisms has also been said to induce oxidative stress by stimulating the process of the formation of reactive oxygen species and leads to irreparable damage to proteins, lipids, or nucleic acids [35]. Moreover, hydroxychavicol is found to have inhibitory activity against the formation of the biofilm, which is a significant factor of virulence related to chronic and relapsing infections [11].

Inhibition of biofilm formation increases vulnerability of bacterial cells to lethal agents of antimicrobial action and may lower the risk of the emergence of antimicrobial resistance. This property makes hydroxychavicol a good candidate for curing persistent infections caused by bacteria, especially those occurring in association with implantation procedures and chronic wounds [11,36]. A number of in vitro experiments have shown that hydroxychavicol has concentration dependent antibacterial activity with low minimum inhibitory concentrations against a broad variety of pathogenic microorganisms [36]. In addition, some studies report synergism of hydroxychavicol and classical antibiotics, which opens the prospect of using this compound as an adjunct to antimicrobial therapy against antimicrobial resistance [7].

With its wide spectrum of activity, ability to act at several targets and natural origin, hydroxychavicol looks like a very promising candidate for developing new formulations of antimicrobial agents. However, lots of in vivo trials on toxicity, pharmacokinetics and well planned clinical studies must be performed before confirming safety and efficacy of hydroxychavicol as a mixed treatment [11,42].

Antifungal Properties:

Hydroxychavicol has exhibited significant antifungal properties against a wide variety of pathogenic fungi, thus establishing it as a potential natural antifungal agent for the management of superficial and systemic fungal infections [12,36]. The rising incidence of fungal infections, together with the increasing resistance to conventional antifungal medications, has heightened interest in the study of bioactive compounds derived from plant material having novel mode of action. Among the various phytochemicals in Piper beetle, hydroxychavicol has always exhibited remarkable inhibitory activity against important fungal species, such as *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Aspergillus niger*, *Aspergillus fumigatus*, and *Trichophyton* species [12,36].

The antifungal properties of hydroxychavicol arise from its ability to damage the integrity of fungal cell membrane and enhance permeability of the membrane, which results in leakage of cellular components and eventual death of the cells. Hydroxychavicol also causes intracellular oxidative stress and disrupts the essential metabolic systems that are necessary for fungal growth and reproduction [12]. All these mechanisms ensure that it is less likely that drug resistance will occur and therefore, hydroxychavicol is effective against many antifungal preparations. Experimental data indicate that hydroxychavicol inhibits the germination of fungal spores, the development of hyphae, and the formation of biofilms, all of which are regarded as important virulence factors for the development of mycosis [36]. The prevention of biofilm development is crucial because fungal biofilms show resistance to many antifungal drugs and result in chronic infections [12].

Many in vitro studies reported low MIC and MFC values of hydroxychavicol on different species of *Candida*, demonstrating its fungicidal and fungistatic properties [36]. Hydroxychavicol also exhibits synergistic activity when used along with some antifungal medications, thus indicating its potential to serve as an adjunctive therapy for improving antifungal drug effectiveness and minimizing the emergence of drug resistance [12]. In summary, these studies show that hydroxychavicol might be a good candidate for the development of its applications in oral medicine, dermatology, and external pharmaceuticals, though it has to be studied in greater detail in vivo, and its pharmacokinetics and clinical applications must also be studied [11,12]

Anti-inflammatory Activity:

Inflammation is a multi-faceted biological response that serves as a protective mechanism for the host from infection and tissue damage, however, uncontrolled or prolonged inflammation is implicated in the development of different chronic diseases like arthritis, heart diseases, diabetes, diseases of the nervous system, and cancers [2,11]. In this context, a lot of scientific studies are carried out with regard to the search for and identification of natural anti-inflammatory agents featuring a good safety profile and multi-target effects. As has been discovered, hydroxychavicol possesses considerable anti-inflammatory activity due to its ability to modify the activity of different molecular and cellular pathways involved in the process of inflammation [11,25]. Scientific experiments have shown that hydroxychavicol prevents the production of pro-inflammatory agents like nitric oxide (NO), prostaglandin E₂ (PGE₂), tumour necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6), thus lowering the level of tissue damage caused by inflammation [25,42].

The anti-inflammatory effect of hydroxychavicol is achieved mainly through the blocking of the most important cellular signal pathways, particularly, nuclear factor-kappa B (NF- κ B) pathway and mitogen-activated protein kinase (MAPK) pathways, which control the expression of numerous inflammatory genes [11,42]. Moreover, it has been revealed that hydroxychavicol can downregulate the activity of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), which are responsible for the synthesis of pro-inflammatory agents [25]. Aside from its ability to inhibit inflammation signalling, hydroxychavicol is also a very effective antioxidant, which is why it plays a role in its anti-inflammatory effect by reducing intracellular reactive oxygen species (ROS) and preventing the cells from suffering oxidative damage [48,50]. Hydroxychavicol has both antioxidant and anti-inflammatory properties, so it may be effective in treating diseases with inflammation.

Moreover, various studies have shown that hydroxychavicol is useful in treating inflammatory skin diseases, inflammatory diseases of the oral cavity, wound healing, and chronic inflammatory diseases [12,25]. However, it is still necessary to carry out detailed in vivo studies and properly executed clinical

tests for scientists to determine its clinical effectiveness, dosage regimen, and safety before it can be used in medicine.

Anticancer Properties:

Cancer continues to top the list of leading causes of death globally thus enforcing the call for the development of safer and more effective drugs. Natural products have significantly taken part in the search for anticancer drugs and hydroxychavicol stands out as one of those natural product candidates as it can affect several signalling types responsible for the initiation, progression, and metastasis of the tumour [11,25]. Numerous in vitro studies have shown that hydroxychavicol can suppress the growth of many human cancer cells including those of colon, oral, breast, prostate, leukaemia, and glioblastoma cancers [25,36].

The anticancer activity is attained through various mechanisms that include apoptosis, induction of cell-cycle arrest, inhibition of angiogenesis, inhibition of tumour cell migration, and oxidative stress modulation [11,25]. Hydroxychavicol induces apoptosis of cancer cells via the activation of intrinsic and extrinsic pathways of apoptosis. It facilitates expression of pro-apoptosis proteins (e.g. Bax) and suppression of anti-apoptotic proteins (e.g. Bcl-2) leading to mitochondrial dysfunction and caspase-mediated cell death [25]. Hydroxychavicol has also been found to affect cell cycle at different stages depending on the target cell type thus restricting uncontrolled cellular division [11].

Antidiabetic Effectiveness:

Diabetes mellitus, a lasting metabolic condition, is characterized by elevated blood glucose levels that result from either dysfunctional insulin secretion or resistance to insulin. The conditions of chronic hyperglycaemia promote oxidative stress, inflammation, and metabolic disorder that in a long run lead to serious complications affecting the cardiovascular, renal, nerve, and eye systems [2,49]. Thus, natural bioactive substances possessing antioxidant and antihyperglycemic effects draw the interest of researchers as potentially useful agents in diabetes treatment. As for hydroxychavicol, it exhibits great potential for the antidiabetic effect due to various mechanisms that promote glucose control and decrease levels of oxidative stress in the organism [11,22]. Thus, the findings of the research have shown that hydroxychavicol improves antioxidant protection of cells and thus safeguards pancreatic beta cells from the damage ensuing from excessive ROS and serving as a significant contributor to the diabetes development [11,48].

The antioxidant influence of hydroxychavicol is complemented by the fact that it has been found to enhance glucose processing through modulation of insulin signalling pathways and alleviating the effects of inflammatory agents involved in insulin resistance [22,25]. A number of preliminary studies have indicated that hydroxychavicol-rich extracts of Piper beetle inhibit carbohydrate-hydrolysing enzymes which leads to a decrease in the amount of glucose absorbed after meals and improvement of glucose metabolism [2,22]. The antidiabetic properties of hydroxychavicol are confirmed by its ability to reduce lipid peroxidation as well as to stimulate the synthesis of the antioxidants produced naturally by the body, like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) which means reduced oxidative tissue damage typically seen in diabetes [48,50]. The aforementioned properties of hydroxychavicol may contribute to the prevention of complications resulting from diabetes.

Despite the increasing amount of research confirming the therapeutic potential of hydroxychavicol in diabetes treatment, the majority of studies have been limited to in vitro and animal tests only. The further research should aim at investigating its pharmacological properties, pharmacokinetics and the effect of hydroxychavicol in clinical settings [11,22].

Wound-Healing Activity:

Wound healing is a coordinated, biological process composed of several different stages like inflammation, cell proliferation, deposition of extracellular matrix, angiogenesis, and tissue remodeling. Any delay in wound healing can be due to microbial infection, excessive oxidative stress, and chronic inflammation; thus, therapeutic agents are needed that can promote healing or speed up tissue repair. Hydroxychavicol has

been known for its potential use for wound healing due to its antioxidant, antimicrobial, and anti-inflammatory properties.

Studies have shown that hydroxychavicol reduces the amount of microorganisms in the wound area and, at the same time, limits tissue damage and inflammatory processes, leading to the creation of favorable conditions for tissue regeneration. It has also been shown to stimulate fibroblast proliferation, collagen formation, and re-epithelization of the tissues, which are important processes during the proliferative phase of wound healing. Its antioxidant properties provide protection of newly regenerated tissues from possible oxidizing agents and thus lead to a faster contraction.

The combined biological characteristics of hydroxychavicol have made it a potential ingredient in topical formulations including wound plasters, hydrogels, transdermal patches and nano-based delivery systems [13]. Despite the promising results obtained in preclinical studies, further research using in vivo and clinical studies is essential to determine the most appropriate dosage, formulation and evaluate tolerability before hydroxychavicol can be used routinely in wound care [11,13].

Molecular Mechanism of Hydroxychavicol:

Modulation of Oxidative Stress:

The pharmacological activity of hydroxychavicol is mainly due to its power of regulating the oxidative stress within cells and ensuring redox balance. It is known that oxidative stress causes excessive formation of reactive oxygen species (ROS), causing the occurrence of lipid peroxidation, protein oxidation, DNA damage, and mitochondrial failure. Serious oxidative stress is highly associated with cancer, diabetes, cardiovascular diseases, neurodegenerative disorders, chronic inflammatory processes.

Hydroxychavicol contains a catechol group with two hydroxyl groups adjacent to each other that helps in scavenging free radicals due to hydrogen atom donation and electron transfer. The properties of hydroxychavicol allow to change superoxide anions, hydroxyl radicals, hydrogen peroxide, and other ROS into non-harmful compounds before they can damage cells.

Apart from direct scavenging, hydroxychavicol also increases the body's endogenous defenses against oxidative stress through activating antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) while lowering the level of lipid peroxidation. Various experimental work has shown that hydroxychavicol acts through the modulation of redox-dependent signalling pathways connected with cell death and inflammation [11,25]. Hydroxychavicol stabilizes redox processes and thus affects numerous pathways involved in apoptosis, inflammation, immunity, and proliferation processes. Its actions can be classified as based on its antioxidant properties.

Control of the Inflammatory Signalling Pathways:

The importance of inflammatory signalling pathways is evident in the development of multiple chronic diseases. Hydroxychavicol has been demonstrated to inhibit inflammation via regulation of significant signalling pathways such as the nuclear factor-kappa B (NF- κ B) signaling and the mitogen-activated protein kinases (MAPK) signalling pathways [11,42].

The NF- κ B activation results in the generation of multiple pro-inflammatory agents such as tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS), thus exacerbating the inflammation [25,42]. The evidence obtained from the experiments showed that hydroxychavicol inhibited activation and nuclear translocation of NF- κ B, which contributed to decreased production of pro-inflammatory agents and inflammation in tissues [25].

Hydroxychavicol has been known to manage various MAPK signalling pathways involving the extracellular signal-regulated kinase (ERK), JNK and p38 MAPK pathways, which take part in cellular growth, organization and differentiation, apoptotic processes and responses to inflammation [11,25]. Hydroxychavicol can either affect generation of notifications and help minimize the inflammatory process in the first place. Simultaneous regulation of both oxidative stress and inflammation signalling pathways illustrates the multidirectional therapeutic effect of hydroxychavicol.

Control of Apoptosis and Progress of the Cell Cycle:

Apoptosis is a controlled mechanism of programmed cell death that is relevant for the preservation of tissue homeostasis by removing cells that are damaged, infected, or altered. Failures in apoptotic signalling lead to cancer initiation and development because the defective cells evade the normal process of cell death and reproduce without any restriction [11,25]. Hydroxychavicol has been shown to exhibit anticancer properties through induction of apoptosis due to several types of molecular mechanisms and prevention of the growth of many cancer cells.

The results of *in vitro* experiments have demonstrated that hydroxychavicol triggers the internal (mitochondrial) pathway of apoptosis by disturbing the mitochondrial membrane potential and facilitating cytochrome c release from the mitochondria into the cytosol [25,36]. After that, the above-mentioned biochemical action will activate the initiator caspase-9 and the executor caspase-3, which will result in DNA fragmentation and apoptotic cell death [25]. Moreover, hydroxychavicol has been revealed to regulate the biosynthesis of proteins of the Bcl-2 family by increasing the expression of pro-apoptotic Bax and reducing the amount of the anti-apoptotic Bcl-2.

In addition to its ability to induce apoptosis, hydroxychavicol also suppresses the proliferation of cancerous cells by stopping the cell cycle at one or more of its checkpoints, thus averting unconstrained cell multiplication [25]. Experimental studies have shown that the repression of the cell cycle occurs at various stages depending on the specific type of cancer, together with decreased expression of cyclins and their activating kinases (CDKs) that regulate the clockwork of the cell cycle [11,25].

Moreover, hydroxychavicol has shown anticancer effects due to its effect on various signal transduction pathways like PI3K/Akt, MAPK, NF- κ B, and STAT3 that regulate such processes as cell survival, proliferation, apoptosis, and angiogenesis [25,42]. Thus, inhibition of these pathways leads to reduced growth of tumors, lesser possibility of metastasis, and increased sensitivity of cancerous cells to apoptosis. Meanwhile, gradual production of moderate amounts of intracellular reactive oxygen species (ROS) inside cancerous cells due to the action of hydroxychavicol was found to lead to mitochondrial dysfunction as well as activation of apoptotic signals without any toxic effects on normal cells [25].

The fact that hydroxychavicol can regulate apoptosis, the cell cycle, oxidative stress, and inflammatory responses at the same time emphasizes its potential to become a multitarget anticancer agent. Nevertheless, although the results of *in vitro* and preclinical trials are encouraging, more clinical studies are required so that the effectiveness, optimum dosage, and safety of this substance for its clinical application can be confirmed [11,25].

Hydroxychavicol is able to modify many different intracellular signaling pathways associated with oxidative stress, inflammation, apoptosis, cell proliferation, and immunity. While conventional medicines usually affect only one molecular target, hydroxychavicol affects interrelated signaling pathways.

One of hydroxychavicol's most important molecular targets is the NF- κ B signaling pathway. This signaling pathway regulates the expression of a variety of genes responsible for inflammation, cell survival, proliferation, and immunity. Hydroxychavicol is known to prevent both activation and translocation of NF- κ B, leading to the downregulation of expressions of inflammatory mediators, such as TNF- α , IL-1 β , and IL-6.

The PI3K/Akt pathway is another important hydroxychavicol target, as it regulates many essential cellular processes, such as survival, proliferation, metabolism, and apoptosis. The dysfunction of PI3K/Akt signaling is a common feature of many cancers and leads to tumor progression. Hydroxychavicol inhibits Akt phosphorylation and promotes apoptosis.

Molecular Targets and Signal Transduction Pathways:

One more significant therapeutic target could be outlined as the mitogen-activated protein kinase (MAPK) signaling pathway. This pathway is composed of three key MAPK enzymes: extracellular signal-regulated kinase (ERK), c-Jun N-terminal Kinase (JNK), and p38 MAPK. Hydroxychavicol regulates these MAPK to affect various cellular responses, such as cell proliferation, differentiation, stress response, and death. If the MAPK signaling pathway is altered, it can further increase the anti-inflammatory and anticancer properties of the molecule.

There is also new evidence showing that hydroxychavicol may influence the Nrf2 signaling pathway. This pathway plays a crucial role in the control of antioxidant defenses in human cells. Once this

pathway is activated, the enzymes that protect cells from stress can be produced, thus helping the cell to cope with oxidative stress.

Thus, the effects of hydroxychavicol involving different pathways such as NF- κ B, PI3K/Akt, MAPK, and Nrf2 leave an impression of a huge potential of hydroxychavicol to be used for various therapeutic purposes.

Advanced Drug Delivery Systems for Hydroxychavicol:

Importance of Advanced Drug Delivery Systems:

In recent times, hydroxychavicol has emerged as an effective phytochemical with a range of pharmacological activities, including antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic, and wound healing activities. Even though hydroxychavicol holds great pharmacological promise, it has limited application in clinical practices primarily due to inadequate physicochemical and pharmacokinetic properties such as low aqueous solubility, vulnerability to oxidation, high metabolic rate, low bioavailability, and insufficient specific site delivery. Such shortcomings in hydroxychavicol prevent effective delivery of therapeutic treatment and therefore demand innovative formulations that would allow maintaining the drug stability and availability for systemic circulation.

Traditional dosage forms (tablets, capsules, topical dosage forms) do not provide sufficient hydroxychavicol concentrations at specific target sites since they get eradicated in a very short time and usually fail to provide desired concentrations. In addition, re-administration of the drug might be required to maintain effective drug levels, which may negatively influence patient adherence to treatment and lead to increased adverse effects. Thus, improving hydroxychavicol pharmaceutical performance is now vital for drug development based on natural products.

In comparison to traditional formulations, advanced drug delivery systems have numerous merits since they enhance drug solubility, safeguard active biological substances from chemical and enzymatic decomposition, lengthen circulation time, facilitate permeability of membranes, and provide drug release in a controlled or targeted manner [13,46]. The use of nano delivery systems improves the surface of active ingredients that favors dissolution, absorption, and effectiveness of therapy while diminishing the dosage needed.

Loss of various nanocarrier systems, including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, ethosomes, nanoemulsions, hydrogels, and transdermal patches have been widely used for the delivery of plant-based active substances [46,47]. These delivery systems allow increased stability of active ingredients, better penetration, controlled release characteristics, and decreased systemic toxicity.

Taking into account its different pharmacological activities as well as impairment faced, hydroxychavicol may be regarded as a good candidate for advanced delivery mechanisms.

The combination of nanotechnology and cutting-edge pharmaceutical carriers should enhance its bioavailability, effectiveness, and usability and result in creation of safe and effective biodegradable products.

Drug Delivery Systems Based on Nanoparticles:

Nanotechnology has been applied to enhance the efficacy of biocompounds with poor properties. Hydroxychavicol has low solubility in water, can be oxidized, and is rapidly metabolized which makes it a candidate for the application of nanotechnology in drug delivery systems [13,25]. It is believed that nanoparticles enhance stability while improving bioavailability and controlling the release mechanisms of drugs thus solving many problems related to conventional types of dosage forms.

Among the various types of nanocarriers polymeric nanoparticles are highly popular ones for carrying phytochemicals due to their qualities such as excellent compatibility, ability to biodegrade and capacity to deliver water-soluble and non-water-soluble substances [46].(i.e.) By encapsulating hydroxychavicol in polymeric nanoparticles the molecule can avoid breakdown before delivering, can stay longer in circulation while releasing drug doses [46,47]. Different lipid carriers have also become widely

popular as vehicles for the delivery of plant phenol compounds [46]. This enables them to have a certain amount of drug per unit weight, to remain stable and go through membranes conveniently.

The smaller size of nanoparticles increases their surface area, which leads to better absorption of drugs [47]. Furthermore, modifying nanoparticles with specific ligands allows for targeted delivery of drugs to diseased organs, thus reducing off-target toxicity and leading to greater specificity. Targeted drug delivery in cancer therapy should help accumulate the hydroxychavicol at the tumour site and improve anticancer action [25,47]. The new data on novel technologies demonstrate that the use of nanoparticles has improved pharmacokinetics and pharmacodynamics of phytochemicals. Thus, the inclusion of hydroxychavicol into nanospheres and liposomes is a promising way of improving its pharmaceutical potential [13,46,47].

Utilization of Liposomes and Ethosomes in Delivering Hydroxychavicol

Both liposomes and ethosomes represent novel vesicular systems for paradigm change in delivering plant products. The use of these drug delivery systems based on lipids allows to increase the solubility of drugs and to stabilize unstable plant substances [13,46]. Given low stability and bioavailability of hydroxychavicol, the above-mentioned systems may serve as promising technologies in preparing relevant formulations of this bioactive.

Liposomes are vesicles composed of a phospholipid bilayer surrounding an aqueous solution. Such lipidic carriers can encompass both lipophilic and hydrophilic compounds, allowing for varying approaches to drug delivery [46]. The process of encapsulating hydroxychavicol permits to prevent its oxidative degradation, improve its stability, and increase its bioavailability. Moreover, the use of liposomes assures generation of sustained release of drugs and reduction of toxicity due to selective localization of drugs.

Ethosomes are a type of vesicle built from lipids which contain high amounts of ethanol, resulting in an increase in flexibility of the membrane and enhanced delivery through the skin [46]. Ethosomes have more efficient transdermal characteristics than standard liposomes since they impinge on the lipid structure of the skin, delivering drugs contained in the vesicles into its deeper layers [46]. Therefore, ethosomes are highly suitable for the skin treatment with hydroxychavicol in cases of fungal infections, wound healing, inflammatory skin diseases and local infections [12,13].

The usage of liposomes and ethosomes for drug delivery of hydroxychavicol may provide improved retention of the drug in the region of administration, provide less frequent administration of the drug, and increased patient compliance due to reduction in the frequency of the drug application [13,46]. Moreover, such vesicular systems allow delaying premature drug degradation and controlling drug delivery. Therefore, the features offered by liposomes and ethosomes are needed in the development of topical and transdermal formulations including phytopharmaceuticals. In general, liposomes and ethosomes can be considered as favorable systems for delivering drugs that have a lot of formulation barriers. Further investigation of ethosomes and liposomes is needed in the field of formulation development, stability evaluation, industrial production process, and clinical trials in order to make these vesicular systems viable in practice.

Hydrogels and Transdermal Drug Delivery Systems:

Hydrogels and transdermal delivery systems are quite good options for the delivery of natural bioactive compounds thanks to their biodegradable nature, the wide potentiality of delivery systems. Hydrogels are three-dimensional structures that allow for the control of the rate of drug release from the active agents locked in them. Hydrogel is a very useful system providing a prolonged life of the drug in its active form and improving its stability and safety for the patient due to the soothing properties of the hydrogel formulation. Hydrogel-based formulations demonstrate all the properties observed for hydrogel use, such as reduced concentration of proteins and bacteria and minimized drug contact with the body. This means that not only can hydrogel-based formulations serve as highly effective holistic treatment modalities but can also help lower the treatment frequency.

Medicated patches and transdermal drug delivery systems are effective methods to deliver hydroxychavicol via skin [13]. Transdermal patches deliver controlled drug release, avoid gastrointestinal

degradation and first-pass metabolism, and keep constant levels of drugs in the bloodstream. Therefore, higher efficiency of hydroxychavicol can be achieved with fewer fluctuations of concentration in conjunction with fewer side effects [46,47].

In addition, new technologies in transdermal medicine, such as microneedles, patches with nanostructures, and stimuli-responsive hydrogels broaden the opportunities for transdermal delivery of plant-based active compounds [46,47].

Combining transdermal medicines and hydroxychavicol may help with drug absorption from skin and lead to successful treatment against fungal infections, inflammatory skin disorders, chronic wounds, and localized diseases. Thus, hydrogel formulations and transdermal systems have great potential in solving the pharmaceutical disadvantages of hydroxychavicol. Further research should be done on the improvement of formulations, stability testing, and other aspects of marketing [13,46].

Future Prospects and Obstacles in Hydroxychavicol Medication Transport:

In spite of having potent pharmacological properties, hydroxychavicol's advancement into approved medicine is still difficult. Factors such as low solubility in water, being subject to oxidation, quick metabolism, low oral bioavailability and reduced clinical support for its use limit its therapeutic value [11,13,25]. Thus, overcoming these limitations is key to producing safe and efficient substances based on hydroxychavicol. Some recent developments in the area of drug delivery technology enable the enhancement of hydroxychavicol transfer by means of advanced multifunctional vehicle systems which eliminate the shortcomings of this medication by ensuring its stability and targeted delivery [46,47].

Thus, the future studies have to concentrate on developing the next generation of drug delivery platforms including nanocarriers that respond to external stimuli, nanocarriers targeted at certain ligands, and biodegradable polymeric systems. One more important field of research is related to search for the optimal parameters of the composition which would contribute to better stability of the mixture with hydroxychavicol [13,46].

In order to facilitate the industrial production scale and its subsequent approval, comprehensive studies should be conducted in the field of formulation compatibility, excipient selection, large-scale manufacturing, and stability investigations. Though many *in vivo* and *in vitro* experiments confirmed the pharmacological properties of hydroxychavicol, the number of clinical trials carried out is still relatively small. The future studies need to focus on pharmacokinetics tests, dose optimization and toxicological evaluation of hydroxychavicol in humans since they would be essential for the confirmation of its safety and efficiency.

Besides, a combination of hydroxychavicol with bioactive phytochemicals or drugs may have synergetic properties, that is expected to lead to less resistance development [7,11]. Moreover, the progress in personalized medicine and nanomedicine may allow for achieving patient- tailored hydroxychavicol formulations. Therefore, the implementation of hydroxychavicol in advanced drug delivery systems and technology is seen as a new opportunity to break through pharmaceutical barriers.

Conclusion

Hydroxychavicol is the major phenolic component of Piper beetle Linn. It has proven to be a promising biologically active natural compound with considerable pharmacological properties and therapeutic potential. Phytochemical and pharmacological studies have shown that hydroxychavicol has strong biological activity, including antioxidant, antibacterial, antifungal, anti-inflammatory, anticancer, antidiabetic, and wound healing properties.

All these activities have been ascribed to hydroxychavicol's potential to modulate oxidative stress, establish an inflammatory response, lead to apoptosis, and activate various intracellular pathways, such as NF- κ B, PI3K/Akt, MAPK, and Nrf2.

However, the application of hydroxychavicol on the clinical field is still limited due to the pharmaceutical limitations associated to its low solubility in water, poor bioavailability, rapid metabolism, and high susceptibility to oxidative degradation. This situation weakens its therapeutic properties and imposes the necessity for the formulation strategies which would allow to overcome the challenges of hydroxychavicol application in medicine. New formulations based on advanced technologies in drug

delivery systems are the new methods for improving the therapeutic characteristics of hydroxychavicol. Various approaches in the introduction of nano-based formulations, liposomes, ethosomes, gels, and transdermal delivery systems can provide a strong support for maintaining physical and chemical stability, controlled release, penetration, and therapeutic properties of Phyto-based products.

The application of hydroxychavicol in all these launched carriers is likely to provide selective delivery, ensure compliance with the therapeutic regimen, decrease the incidence of adverse reactions, and lead to better results of the treatment [13,46,47].

Despite the significant achievements made in vitro and preclinically, it is necessary to obtain more scientific evidence regarding hydroxychavicol for its clinical use. It is crucial to carry out studies aimed at pharmacokinetics of hydroxychavicol, toxicity testing for a long time, formulation development, and large-scale production of hydroxychavicol-based products, and performing clinical trials. In addition, a combination of different disciplines such as phytochemistry, nanotechnologies, pharmaceutical sciences, and clinical medicine is essential for the introduction of standardized formulations based on hydroxychavicol.

Thus, hydroxychavicol can be considered one of the most promising phytopharmaceutical candidates possessing different biological activities and a high potential for drug development.

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