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Review Article

Natural sources for coumarins and their derivatives with relevance to health-promoting properties: A systematic review

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ABSTRACT

Coumarins and their derivatives are bioactive compounds recognized for their diverse range of health-promoting properties. This systematic review aims to identify and summarize the natural sources of coumarins and their derivatives. Electronic databases, including PubMed, Scopus, and Web of Science, were thoroughly searched with precise keywords and inclusion/exclusion criteria. Studies published in English from 2000 to 2023 were considered for inclusion. Natural sources of coumarins and their derivatives were identified, including plants, fungi, and bacteria. Some common plant families known to contain coumarins and their derivatives were Asteraceae, Rutaceae, and Fabaceae. The health-promoting properties of coumarins and their derivatives were found to be extensive. Many studies have reported their antioxidant, anti-inflammatory, anticancer, antibacterial, and antifungal activities. The compounds have shown potential in protecting against cardiovascular diseases, neurodegenerative disorders, diabetes, and obesity. Understanding the structure-activity relationships of these compounds is crucial for further research and development in this area.

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1. Introduction

Coumarins are organic compounds characterized by their coumarin ring structure. They can be found naturally in various plants or synthesized in laboratories. The Tonka bean (*Dipteryx odorata*), from which coumarin was first isolated in 1820 by Vogel, is known in French as "coumarou," which inspired the name "coumarin". Subsequently, coumarin was identified in a range of other plants, including strawberry, lavender, black currant, apricot, and cherry, as well as sweet clover, cassia leaf oil (up to 87,300 ppm), woodruff, bison grass, vanilla grass, and cinnamon bark oil (7,000 ppm) (Robe et al., 2021). The Rutaceae and Umbelliferae families are the primary sources of coumarins, which are predominantly found in higher plants. Although coumarins are present in all parts of the plant, they are most abundant in the fruits, followed by the roots, stems, and leaves. The concentration of coumarins in different plant sections can be influenced by seasonal variations and environmental factors (Anatheil et al., 2022). Being secondary metabolites, these substances protect plants from infections and play a specific role in photosynthesis, respiration regulation, and the activity of plant growth hormones and regulators.

In nature, coumarin and its derivatives can be found in their free form or as glycosides, having been conjugated with other molecules. In the quantities present in edible plants, the majority of these substances are not considered a threat to human health (Sharifi-Rad et al., 2021).

Derivatives of coumarins encompass compounds with various functional groups attached to the coumarin core, including hydroxylated, methoxylated, prenylated, and glycosylated coumarins. Notable examples of these derivatives are umbelliferone, warfarin, and esculin. Coumarins, also known as benzopyrones or 1,2-benzopyrones (or 2H-1-benzopyran-2-ones),

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are naturally occurring compounds characterized by the fusion of a benzene ring with a pyrone ring. Natural coumarins can be classified into six primary groups, namely simple coumarins, biscoumarins, benzocoumarins, linear and angular pyranocoumarins, linear and angular furanocoumarins, and coumestans (Lončar et al., 2020).

Coumarins and their derivatives have a wide range of applications. Some common uses include medicinal applications, such as warfarin, which is used as an anticoagulant medication to prevent blood clots. Additionally, coumarins demonstrate potential in cancer treatment due to their cytotoxic properties (Sun et al., 2020). Coumarins, such as 4-methylcoumarin, are utilized in fragrances and flavorings. They are commonly found in perfumes and serve as flavoring agents in the food and beverage industry (Lončar et al., 2020). Coumarin derivatives can also function as sunscreen agents, providing protection against harmful UV radiation (Kurzawa et al., 2022).

Other coumarin derivatives have been investigated for their insecticidal and antifungal properties, positioning them as potential candidates for agricultural applications. Coumarin has been used as a fragrant ingredient in a variety of cosmetic products, including shower gels, shampoos, toothpaste, soaps, intimate cleansers, shaving foams, body creams, facial creams, hand creams, deodorants, sunscreens, aftershaves, and lipsticks. In addition, it has been incorporated into tobacco products to enhance their flavor and aroma, ultimately making them more appealing to consumers. Following its synthesis in 1868, coumarin was first introduced to the market as a flavoring agent (Lončar et al., 2020).

Several coumarin compounds are actively being researched as potential medication candidates for treating a variety of disorders. These substances demonstrate excellent pharmacological activity, minimal toxicity and adverse effects, low drug resistance, high bioavailability, a wide therapeutic index, and exceptional curative effects. Consequently, they have been utilized in various pharmacological applications, including antibacterial drugs, antioxidants, anti-inflammatory agents, anti-HIV treatments, anticancer therapies, anticoagulants, antiviral medications, and anti-tuberculosis agents (Peng et al., 2013). The use of coumarin as a flavoring ingredient has come under scrutiny after studies revealed that rats and dogs fed a coumarin-containing diet experienced liver damage. However, it has not yet been determined whether coumarin has a genotoxic effect on humans. Subsequent studies have suggested that coumarin may be linked to cancer (Hsieh et al., 2019).

The future prospects of coumarins are promising, with ongoing research and discoveries. Scientists are exploring new derivatives and investigating their potential therapeutic applications. Moreover, efforts are being made to modify the properties of coumarins to enhance their biological activity and reduce potential side effects. Coumarins also serve as valuable scaffolds in the development of new drugs, with various derivatives being synthesized and tested for different medical conditions. Overall, the study of coumarins and their derivatives continues to expand, revealing their wide-ranging applications across various fields, including medicine, agriculture, and cosmetics. This systematic review aims to identify and summarize the natural sources of coumarins and their derivatives.

2. Methodology

In preparing the present review, we meticulously gathered relevant scientific papers from various reputable databases, including Google Scholar, ScienceDirect, MDPI, Web of Science, and PubMed. Our search was guided by specific keywords such as 'anti-inflammatory', 'coumarin', 'furanocoumarin', 'neurodegenerative disorders', 'secondary metabolites', 'pharmacological', 'pyranocoumarins', and 'warfarin'. The selection process was rigorous, and we carefully evaluated each article based on its scientific validity and significance. Our primary focus was on studies exploring the beneficial properties of coumarin. To maintain consistency, we restricted our search to studies published in English. This comprehensive review was meticulously prepared in January 2024, ensuring that it reflects the most current research.

3. Coumarins sources

Coumarin is present in various plant sources, including those from the Apiaceae, Fabaceae, Moraceae, and Rutaceae families. It has a distinct sweet, hay-like odor (Goncalves et al., 2020). The main natural sources of coumarin include:

3.1. Tonka beans

These are the seeds of the *Dipteryx odorata* tree, which is native to South America. Tonka beans are renowned for their high coumarin content, which imparts a distinctive vanilla-like aroma. They are frequently utilized in both perfumery and culinary applications (Adimule et al., 2022).

3.2. Sweet woodruff

This perennial plant, known scientifically as *Galium odoratum*, is native to Europe and Asia. It is commonly used as a flavoring agent in beverages and desserts. Sweet woodruff contains substantial amounts of coumarin and emits a pleasant, sweet aroma when dried (Alm, 2015).

3.3. *Cassia cinnamon*

While true cinnamon (*Cinnamomum verum*) contains very low levels of coumarin, cassia cinnamon (*Cinnamomum cassia*) has significantly higher amounts. Cassia cinnamon is commonly used in baking and cooking and has a more intense, slightly spicy flavor compared to true cinnamon (Senevirathne et al., 2022).

3.4. Mullein

Also known as *Verbascum*, mullein is a tall, flowering

plant native to Europe, Asia, and North Africa. The leaves and flowers of some mullein species contain coumarin. This plant is often used in traditional medicine for its expectorant and anti-inflammatory properties (Alamgir, 2017).

3.5. Sweet clover

Sweet clover, scientifically known as Melilotus, is a flowering plant that thrives in temperate regions worldwide. It is commonly utilized as a forage crop for livestock because of its high protein content. Certain species of sweet clover, especially yellow sweet clover (*Melilotus officinalis*), contain coumarin, which has various applications. Additionally, sweet clover is used to make herbal tea and is valued in traditional medicine (Ruiz et al., 2022).

3.6. Woodruff

Woodruff refers to several species within the genus *Galium*. It is commonly used as a flavoring ingredient in European liqueurs, such as the German beverage known as Maiwein. Woodruff has a sweet aroma and contains coumarin (Al-Zehouri, 2017).

3.7. Lavender

Lavender (*Lavandula*) is a popular flowering plant native to the Mediterranean region, widely known for its fragrant flowers and essential oils. Some species of lavender, such as *Lavandula stoechas*, contain small amounts of coumarin. (Aprotosoaie et al., 2017; Ez zoubi et al., 2020).

While coumarin is found in various natural sources, it can also be chemically synthesized and utilized as a flavoring agent or fragrance compound in a range of products. However, due to potential health concerns associated with high coumarin intake, natural sources are regarded as safer alternatives.

4. Classification of coumarins

Calophyllum dispar (Clusiaceae) fruits and stem bark have recently yielded six novel minor coumarins. The genus *Calophyllum* approximately involves around 200 species, many of which are utilized in traditional medicine and found throughout tropical rainforests. While the majority of known natural coumarins are produced by higher plants, some have also been identified in microbial sources. Notable coumarin compounds, such as novobiocin and coumermycin from Streptomyces, as well as from *Aspergillus* species, have been discovered in these microorganisms. Among these, aflatoxin B1 is the most prevalent and is classified as a highly toxic fungal metabolite (Shaik et al., 2019).

Six basic groups of natural coumarins (Fig. 1) include simple coumarins, furanocoumarins (linear type), furanocoumarins (angular type), benzoylcoumarins, pyranocoumarins (linear type), pyranocoumarins (angular type, Fig. 2), biscoumarins, and coumestans (Borges et al., 2010).

The five-membered furan ring of a furanocoumarin, which can be either linear or angular in structure and may contain substituents at one or both of the remaining benzoid positions, is linked to the coumarin nucleus. Certain plants produce a class of chemical compounds known as furanocoumarins as a defense mechanism against external threats. Furanocoumarins are important due to their impact on the metabolism of certain drugs (Berenbaum, 2002).

They inhibit the liver enzyme cytochrome P450, which prevents the metabolism of certain drugs. Examples of furanocoumarin subtypes include bergamottin, dihydroxybergamottin, bergapten, isobergapten, angelicin, and psoralen. Bergamottin and dihydroxybergamottin are prevalent in grapefruit, while Seville oranges and pomelos also contain significant levels of these compounds. Figs are known to contain psoralen. Furthermore, bergapten and psoralen are abundant in celery, isobergapten and psoralen are found in parsnips, and psoralen is present in fennel seeds, parsley, and wild carrot. Members of the pyranocoumarin family resemble furanocoumarins but feature a six-membered ring instead. 4-Hydroxycoumarin is one of the coumarins that is substituted in the pyrone ring (Bhattarai et al., 2021).

Psoralen is effective in treating several skin conditions, including vitiligo, alopecia, and psoriasis. This natural compound, found in certain plants, has been extensively studied for its pharmaceutical properties. It is primarily recognized for its role in phototherapy, particularly in the management of skin disorders such as vitiligo and psoriasis. Psoralen enhances the skin's sensitivity to ultraviolet (UV) radiation, which can help slow the rapid turnover of skin cells and reduce inflammation. As a result, patients may experience improvements in symptoms such as redness, scaling, and patchiness. However, psoralen must be applied under medical supervision due to potential side effects, and it should be used with caution. Bergapten, also known as 5-methoxypsoralen, is a naturally occurring compound found in some plants and is part of the psoralen family. This group of chemicals includes the synthetic drug warfarin. Coumarin, the parent compound of this group, has been designated as the head of the benzo-a-pyrones due to its structural simplicity, although it is commonly believed that 7-hydroxycoumarin should be considered the parent component of the more complex coumarins (Nisha et al., 2021).

Warfarin is a widely used anticoagulant medication that helps prevent the formation of blood clots. It works by inhibiting the liver's production of specific clotting factors, namely factors II, VII, IX, and X, along with proteins C and S. By decreasing the activity of these clotting factors, warfarin prolongs the time it takes for blood to clot, thereby helping to prevent the development of potentially harmful blood clots (Wang and Yao, 2022). In individuals with certain medical conditions, warfarin primarily functions to reduce the risks of deep vein thrombosis (DVT), pulmonary embolism (PE), and other thromboembolic events, as well as strokes associated with atrial fibrillation, mechanical heart valves, or a history of blood clots. However, it is important to note that warfarin is a potent medication that requires careful monitoring. Its effectiveness can be influenced by

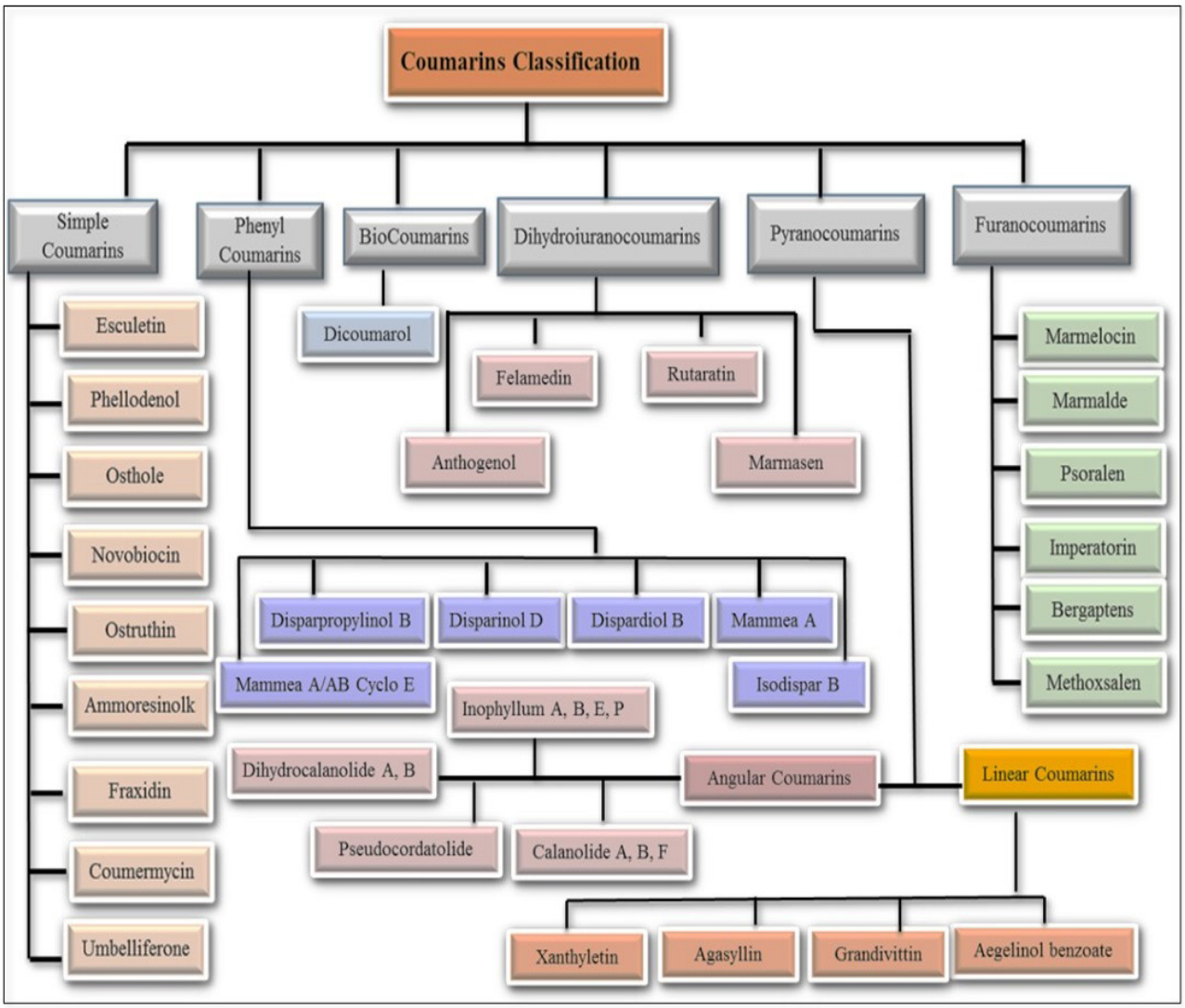

Fig. 1. Classification of coumarins and coumarin derivatives.

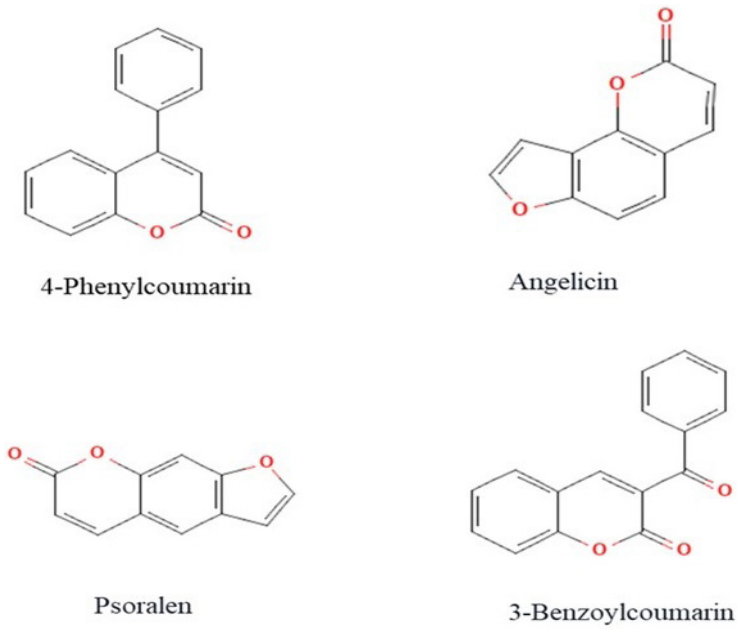

Fig. 2. Structures of coumarin 4-phenyloumarn, benzoylcoumarins, psoralen and angelicin.

various factors, including diet, other medications, and individual responses. Regular monitoring of a patient's blood clotting time, measured as the International Normalized Ratio (INR), is essential to ensure proper dosing and minimize the risk of bleeding complications. As with any medication, it is crucial for patients using warfarin to closely follow their healthcare provider's instructions and communicate any concerns or potential interactions with other medications or lifestyle changes (Niederberger and Parnham, 2021).

Isoflavones, known as benzo-g-pyrones, include genistein. This naturally occurring component of soy has been extensively researched as a chemopreventive agent, primarily in animal models of hormonally influenced breast and prostate cancers (Shaheen et al., 2022).

Regarding the pharmacological effects of genistein, it is important to note that while it has been researched for potential health benefits, it is not approved or regulated as a pharmaceutical by authorities such as the FDA. Genistein, a natural compound found in soy and other plants, has been investigated for its potential effects in various areas, including hormone-related conditions and cancer prevention or treatment. However, research on genistein is still evolving, and its clinical applications and optimal dosage have yet to be conclusively established (Nazari-Khanamiri and Ghasemnejad-Berenji, 2021).

Diverse biological activities of substituted coumarin derivatives have been documented. Coumarin derivatives serve as the active components in potent antibiotics, including novobiocin, coumaromycin, and chartesium. Recently, interest in these compounds has been renewed due to their use as fluorescent markers in the biochemical identification of enzymes. Various methods for synthesizing coumarin derivatives include the Claisen rearrangement, Perkin reaction, Pechmann reaction, Wittig reaction, and Knoevenagel condensation (Nisha et al., 2021).

Examples of derivatives of coumarins include 7-hydroxycoumarin, which contains a hydroxyl group (-OH) attached to the 7th carbon atom of the coumarin ring. It is commonly known as umbelliferone which is found in plants such as umbellifers. Another derivative, 4-methylcoumarin, has a methyl group (-CH_3) attached to the 4th carbon atom of the coumarin ring (Fig. 3). This synthetic compound is often used as a fragrance or flavoring agent. The warfarin derivative, a 4-hydroxycoumarin, is widely used as an anticoagulant medication and acts as a vitamin K antagonist. Esculin, a glycosylated coumarin, has a sugar molecule attached to it. It is commonly found in horse chestnut trees and is used in some skincare products (Mazreku et al., 2022). Whereas prenylated coumarin derivatives have prenyl (C_5H_8) groups attached to the coumarin ring. Examples include osthol, which is found in various medicinal plants, and xanthotoxin, which is found in plants such as parsley and celery (Olennikov, 2022).

Many plant species' seeds, roots, and leaves naturally contain derivatives of coumarins, which are secondary metabolites. It has become evident that microwave irradiation is highly effective in accelerating and streamlining various condensation processes, which can be conducted both in the presence of a solvent and in its absence. The primary focus of this research was to compare microwave irradiation with traditional techniques for the production of coumarin derivatives (Nawrot-Chorabik et al., 2022).

Studies have demonstrated the potential of certain compounds, such as benzocoumarins and 3-heteroaryl substituted coumarins, as adaptable biodynamic agents that may be useful in medicine and as photochromic dyes. Similarly, other coumarin chalcones in solvent-free environments exhibit strong antibacterial activity. Coumarin compounds represent an important class of oxygen-containing heterocyclic moieties originally identified as secondary metabolites in various microorganisms and plants. Numerous organic compounds containing coumarin as a fundamental unit have been discovered, leading to significant applications, including anti-inflammatory, antibacterial, analgesic, antifungal, antioxidant, anticancer, antimicrobial, and anti-HIV properties. In addition to these applications, coumarin compounds are widely utilized in other fields, such as the food and dye industries, as well as in fragrances and cosmetics (Bouhaoui et al., 2021).

5. Role of coumarin as a therapeutic agent

5.1. Role of coumarin in AIDS therapy

Recent research has highlighted the potential of coumarin derivatives for use in AIDS (Acquired Immunodeficiency Syndrome) therapy regimens. Warfarin derivatives offer two advantages over other potential HIV treatment candidates: i) They exhibit non-toxic effects on cells, and ii) their pharmacology is well-documented, facilitating clinical trials. Warfarin, 4-hydroxycoumarin, and 7-hydroxycoumarin have all been shown to significantly inhibit HIV replication in lymphocytes after a single dose (Menezes and Diederich, 2019). Coumarin acts by:

5.1.1. Inhibition of HIV reverse transcriptase (RT) and integrase

Certain coumarins directly inhibit the activity of HIV reverse transcriptase (RT), a crucial enzyme involved in viral replication. By interfering with RT, these compounds prevent the conversion of viral RNA into DNA, thereby hindering the virus's ability to integrate into the host genome. Specific coumarins can inhibit HIV integrase, another essential enzyme responsible for viral integration. By blocking integrase, they disrupt the integration process and limit the spread of the virus (Sharapov et al., 2023).

5.1.2. Regulation of cellular factors

Coumarins derived from plant sources can modulate cellular factors involved in regulating HIV-1 replication. These compounds may influence host cell proteins associated with viral transcription, translation, or assembly. By targeting these cellular factors, coumarins indirectly suppress viral replication.

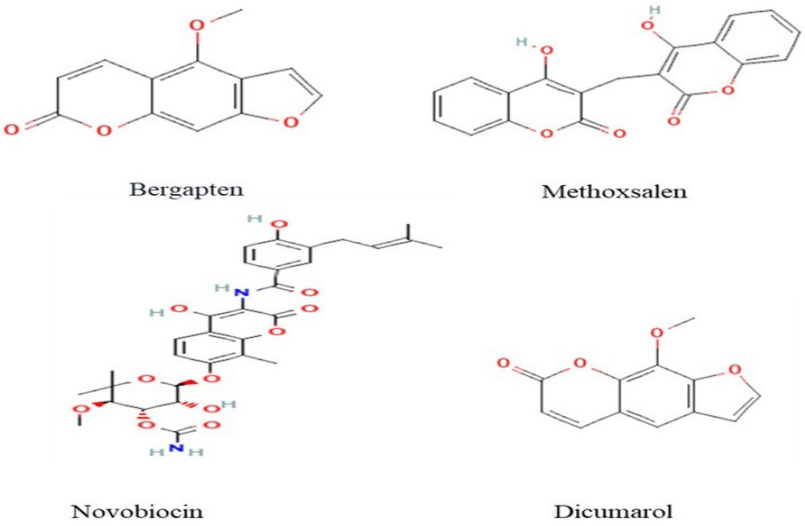

Fig. 3. Structure of coumarin derivatives, bergapten, novobiocin, methoxsalen and discoumarol.

5.1.3. Transmission of viral particles

Some pyranocoumarins, a specific subclass of coumarins, exhibit multiple mechanisms of action. They can bind to various sites, making them resistant to HIV mutations. Certain coumarins also interfere with the transmission of viral particles from infected macrophages to healthy cells, thereby limiting the virus's spread within the body.

5.1.4. Safety considerations

While unsubstituted coumarin can be hepatotoxic, oxygenated coumarin derivatives—such as those found in plants—generally exhibit low toxicity. This characteristic makes them suitable candidates for combination therapies. Researchers have investigated hydroxyl-containing coumarins synthesized through Pechmann condensation as potential antiretroviral agents (Sharapov et al., 2023).

5.2. Cancer therapies

One of the most significant and widespread causes of mortality worldwide is cancer (Aberoumandi et al., 2017; Fathi Karkan et al., 2017; Nekoei et al., 2021; Mahdavi and Mohammadhosseini, 2022). Historically, anti-cancer medications have been designed to target and damage abnormally dividing cells by inhibiting cell division. Combination therapies, which utilize multiple cytotoxic drugs within a single treatment regimen, often yield better outcomes with fewer adverse side effects. This is achieved through careful management that allows normal cells—unlike malignant ones—to recover from drug exposure (Pangal et al., 2022). The quest for new and efficient methods to enhance existing treatments has proven to be relentless, as current medications are unable to significantly extend patients' expected lifespans. Reports indicate that these drugs have demonstrated objective responses in some patients with advanced malignancies, which has sparked interest in coumarin and 7-hydroxycoumarin as potential anti-cancer agents (Perumalsamy et al., 2018; Pangal et al., 2023-). The mechanism of action is as follows (Wu et al., 2020).

5.2.1. Inhibition of carbonic anhydrase (CA)

Coumarins can inhibit the activity of carbonic anhydrase, an enzyme that plays a crucial role in maintaining pH balance within cells. By inhibiting suppressing carbonic anhydrase, coumarins disrupt the acidic microenvironment that supports promotes growth (Banikazemi et al., 2021).

5.2.2. Targeting PI3K/Akt/mTOR signaling pathways

Coumarins may disrupt the PI3K/Akt/mTOR pathway, which is essential for cell survival, proliferation, and angiogenesis. By modulating this pathway, coumarins hinder cancer cell growth and survival (Wu et al., 2020).

5.2.3. Induction of cell apoptosis

Coumarins promote programmed cell death (apoptosis) in cancer cells by activating apoptotic pathways. This activation leads cell demise and helps prevent uncontrolled proliferation.

5.2.3. Suppression of tumor multidrug resistance (MDR)

Some coumarins can counteract multidrug resistance mechanisms in cancer cells. By inhibiting the efflux pumps responsible for drug resistance, they enhance the effectiveness of chemotherapy.

5.2.4. Inhibition of microtubule polymerization

Certain coumarins disrupt microtubule assembly, hindering cell division and inhibiting tumor growth.

5.2.5. Regulation of reactive oxygen species (ROS)

Coumarins can modulate reactive oxygen species (ROS) levels within cancer cells. Proper ROS regulation is essential for maintaining cellular homeostasis, and coumarins may exploit leverage balance to exert their effects.

5.2.6. Inhibition of tumor angiogenesis

Coumarins may inhibit the formation of new blood vessels (angiogenesis) necessary for tumor growth. By targeting angiogenic factors, they restrict tumor's blood supply.

5.3. Coumarin in malignant melanoma

A favorable prognosis can be achieved, and surgical excision of the original lesion is facilitated by the early identification of malignant melanoma. However, if the lesion progresses, the likelihood of recurrence increases, posing a significant challenge to oncologists, as there is currently no effective treatment for recurrent malignant melanoma (Fallico et al., 2021). Research on the use of warfarin as a conservation medication in the treatment of melanoma with coumarin derivatives has highlighted its potential to inhibit tumor metastasis and stimulate the activity of granulocytes, lymphocytes, and macrophages (Shaheen et al., 2022).

Contrary to warfarin, coumarin does not possess anticoagulant properties, and Riordan's earlier use of it resulted in a subjective improvement among cancer patients. Coumarin is non-toxic and easy to administer. In a small-scale study, patients with stage IB lesions (more than 1.70 mm in thickness) and stage II melanomas following primary resection were treated with either coumarin or warfarin. Six individuals received 25 mg of coumarin daily, while five patients were administered warfarin as an anticoagulant. One patient in each group experienced a recurrence within the first year, and the therapeutic efficacy of coumarin was found to be comparable to that of warfarin.

5.4. Coumarin in renal cell carcinoma

Over the past 20 years, neither hormone therapy nor chemotherapy has been able to improve survival rates for patients with metastatic lesions. Currently, there is no cure for renal cell carcinoma (Küpeli Akkol et al., 2020; Shaheen et al., 2022). Reports of the immunomodulatory effects of coumarins and their potential use in treating malignant melanoma have raised concerns about the coumarin family of compounds as a viable treatment option (Soleimanjahi and Habibian, 2020; Bhattarai et al., 2021). Coumarin was administered orally in a single dose, and on day 15, cimetidine [4 doses of 300 mg daily] was added to the treatment regimen. The most common adverse effect, nausea, was well tolerated at all coumarin levels, likely due to the strong fragrance of coumarin. Seven patients with renal cell carcinoma exhibited objective responses, which were observed at dosages ranging from 600 to 5000 mg of coumarin.

5.5. Coumarin in prostate cancer

Prostate cancer is characterized by a relatively slow rate of progression and a wide range of biological diversity, particularly regarding hormone sensitivity. A small-scale study was conducted to evaluate the effectiveness of coumarin in treating prostate cancer, as it has previously demonstrated immunomodulatory effects in other malignancies. During the experiment, 14 patients received a single oral dose of 1 mg of coumarin daily. Starting on day 15, 300 mg of cimetidine were added to the treatment regimen. Both medications were continued until disease progression was observed. Although there were no significant objective effects, patients reported a substantial subjective reduction in their bone pain. Approximately, 40 patients with metastatic, hormone-naive, or hormone-refractory prostate cancer participated in a phase I study. Participants received 3.0 g of coumarin daily, and their toxicity and anti-tumor responses were assessed. In this research, partial responses were observed in all patients with modest tumor burdens. One responder maintained responsive bone metastases and stable prostate-specific antigen (PSA) levels for seven years following the study. Based on these findings, a multi-center trial supervised by the US FDA has been initiated to investigate the role of coumarin in metastatic (stage M1) prostate cancer (Küpeli Akkol et al., 2020; Pourbagher-Shahri et al., 2022).

Another study investigated 80 patients with either hormone-naive or hormone-independent metastatic illness (Group A) to assess the effects of 1.0 g of coumarin taken daily. However, 80 more patients with confirmed micrometastases following prostatectomy will participate in a trial where they will be randomly assigned to receive either a placebo or 1.0 g of coumarin daily (Group B). In the most recent report, 24 patients in Group A have been enrolled, and only 1 has not experienced disease progression after 54 months. In Group B, 40 patients have been registered to date, with 8 patients receiving coumarin and 9 patients receiving the placebo (Singla et al., 2021).

5.6. Immunomodulatory effects

Both *in vitro* and *in vivo* experiments have demonstrated that coumarin enhances the expression of human leukocyte antigen (HLA) DR and DQ antigens on peripheral blood monocytes, indicating an activated cell state. Coumarin also activates natural killer cells and macrophages. Furthermore, it increases the TH: Ts cell ratio *in vitro*. It is also noteworthy that coumarin promotes the activation of monocytes by lipopolysaccharide, leading to the production of inflammatory cytokines. Consequently, it is believed that coumarin enhances the activation of immune system cells, particularly within the monocyte/macrophage lineage, potentially increasing their tumoricidal activity *in vivo* (Sharifi-Rad et al., 2023).

5.7. Chemopreventive effects

Chemoprevention is the process of preventing cancer development by administering substances that mitigate the effects of exposure to carcinogenic agents. Currently, 30 families of compounds have been identified as possessing anticancer properties. These substances include phenolic antioxidants, flavonoids, indoles, cinnamates, and coumarins. The ability of animal cells to enzymatically inactivate reactive electrophilic forms of carcinogens is believed to be the source of their anti-carcinogenic properties. This is achieved by enhancing the activity of phase II xenobiotic-metabolizing enzymes, such as UDP (uridine diphosphate) glucuronosyltransferases, glutathione S-transferases (GST), and quinone reductases. In rodent tissues, coumarin increases GST levels and inhibits hydrocarbon-mediated carcinogenesis and subsequently, in a mouse hepatoma cell line, it elevates quinone reductase levels (Wu et al., 2009).

6. Pharmacological activities of coumarins

The capacity of coumarins to scavenge free radicals and reduce oxidative stress is well established. They possess antioxidant properties that help protect cells and tissues from damage caused by ROS. Moreover, they have been found to exhibit anti-inflammatory activities by inhibiting inflammatory mediators and pathways. In various inflammatory disorders, coumarins can help alleviate inflammation and related symptoms (He et al., 2017).

Many coumarins have demonstrated anticancer properties by exerting cytotoxic effects on cancer cells and inhibiting tumor growth. They can induce apoptosis, inhibit cancer cell proliferation, and disrupt angiogenesis. Coumarins possess antimicrobial properties against various bacteria, fungi, and viruses. They can inhibit the growth and replication of microorganisms, making them potentially valuable in combating infections (Önder, 2020). Some coumarins exhibit anticoagulant and antiplatelet properties. They can interfere with blood clotting mechanisms, potentially reducing the risk of thrombosis and related cardiovascular disorders. Certain coumarins have demonstrated neuroprotective effects, safeguarding neuronal cells from damage and promoting overall brain health. They may enhance cognitive function and could be beneficial in the treatment of neurodegenerative diseases (Razak et al., 2023).

Coumarins have been linked to various cardiovascular benefits, including vasodilation, reduced blood pressure, and protection against cardiac disorders. They can positively influence lipid profiles and contribute to overall cardiovascular health. Some coumarins have also shown antidiabetic properties by enhancing insulin sensitivity, improving glucose metabolism, and regulating blood sugar levels, making them potentially beneficial for diabetes management. It is important to note that the specific pharmacological effects of coumarins depend on their structure, concentration, and the biological system under investigation. Further research is necessary to fully understand the mechanisms of action and to optimize the therapeutic potential of coumarins in various health conditions.

6.1. Anti-inflammatory activity

Coumarin, a bioactive compound found in various natural sources, is recognized for its anti-inflammatory properties. Numerous studies have demonstrated that coumarin can reduce inflammatory processes and alleviate symptoms associated with inflammation. It exerts its anti-inflammatory effects by modulating various inflammatory pathways and mediators. Specifically, coumarin inhibits the production and release of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). Furthermore, coumarin can inhibit inflammatory enzymes, including cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and nitric oxide synthase (NOS). Furthermore, coumarin exhibits antioxidant properties, which further enhance its anti-inflammatory activity by scavenging free radicals and reducing oxidative stress, a key contributor to inflammation (Fan et al., 2022).

Several *in vitro* and *in vivo* studies have demonstrated the anti-inflammatory effects of coumarin across various models of inflammation, including both acute and chronic conditions. Coumarin has proven effective in reducing inflammatory markers, edema, and tissue damage in these models. Furthermore, the anti-inflammatory properties of coumarin have been investigated in relation to inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, and asthma. In a rat model of colitis induced by trinitrobenzene sulfonic acid, esculetin, another derivative of coumarin, exhibited significant anti-inflammatory activity (Abdul Khaliq et al., 2022). Imperatorin, a coumarin-derived compound with anti-inflammatory properties, is also known to inhibit the lipoxygenase and cyclooxygenase enzymes, as well as to suppress the formation of superoxide anions in neutrophils (Hassanein et al., 2020).

In these conditions, coumarin has demonstrated potential in reducing inflammation and alleviating disease symptoms (Mahmoud et al., 2019). Despite the promising findings, it is essential to conduct further research to fully understand the mechanisms of action and optimize the therapeutic potential of coumarin as an anti-inflammatory agent. However, more studies are needed to evaluate the safety and efficacy of coumarin in human subjects, taking into account factors such as dosage, formulation, and potential drug interactions.

6.2. Anticoagulant activity

Recent studies have provided valuable insights into the anticoagulant activity of coumarin and its derivatives. By inhibiting the interconversion of vitamin K and the vitamin K epoxide cycle, as well as inducing the hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity, coumarins exhibit antivitamin K effects. Numerous coumarin derivatives, including warfarin and dicoumarol, possess anticoagulant properties (Kasperkiewicz et al., 2020).

Coumarin-based compounds, such as warfarin and acenocoumarol, have long been utilized as oral anticoagulants to prevent blood clotting and reduce the risk of thromboembolic events. These coumarin derivatives exert their anticoagulant effects by inhibiting the synthesis of vitamin K-dependent clotting factors, primarily factors II, VII, IX, and X. By disrupting the production of these clotting factors, coumarins hinder the clotting cascade and delay the formation of blood clots (Chen et al., 2022).

Recent studies have concentrated on optimizing the therapeutic application of coumarin-based anticoagulants. Innovative formulations and delivery methods, such as nanoparticles and targeted drug delivery systems, have been found to enhance the efficacy and safety of these agents. Additionally, research has explored the pharmacodynamics and pharmacokinetics of coumarins to refine their dosing regimens and minimize the risk of adverse effects. Furthermore, investigations have focused on identifying potential predictive biomarkers for monitoring the anticoagulant effects of coumarin therapy.

Genetic variations, such as polymorphisms in specific genes, have been studied to understand inter-individual variability in response to coumarins and to guide personalized dosing strategies. While coumarin-based anticoagulants have demonstrated efficacy, they also present certain limitations. Their narrow therapeutic index necessitates regular monitoring and dose adjustments to maintain the desired anticoagulant effect without increasing the risk of bleeding complications. Furthermore, coumarins interact with various drugs and foods, which requires caution and careful management during therapy. Overall, recent studies on the anticoagulant activity of coumarins have focused on optimizing treatment protocols, enhancing drug delivery, and identifying predictive biomarkers. These advancements aim to improve the efficacy, safety, and individualization of coumarin-based anticoagulant therapy.

6.3. Antibacterial activity

Coumarins are compounds known for their antibacterial properties. They can disrupt bacterial cell membranes and inhibit bacterial growth. It has been well-documented that coumarins interfere with bacterial DNA replication and transcription processes, preventing bacteria from replicating or expressing essential genes required for survival (Feng et al., 2020). Coumarins can bind to specific proteins in bacteria, inhibiting their proper function and ultimately leading to cell death. It is worth mentioning that coumarins may stimulate an immune response against certain types of bacteria by activating macrophages and other white blood cells that are responsible for combating infections (Gupta and Birdi, 2017). Against both Gram-positive and Gram-negative bacterial strains, coumarin derivatives have been documented in the literature to possess a broad spectrum of antibacterial activity. *Staphylococcus aureus*, *Bacillus megaterium*, *Micrococcus lysodeikticus*, and ammoresinol, among others, are susceptible to the effects of andostruthin. Another coumarin derivative, anthogenol, demonstrated antibacterial activity against *Enterococcus*.

6.4. Antifungal activity

Coumarins are compounds known to exhibit antifungal activity. They can inhibit fungal growth by disrupting cell membranes and interfering with enzymes involved in metabolic processes (Jha and Mohamed, 2022). They also function as fungistatic agents, meaning they prevent fungi from growing or reproducing without killing them outright. Coumarins can also disrupt the production of ergosterol, a crucial component of fungal cell membranes, leading to increased permeability and the eventual death of fungal cells. According to the literature, coumarins have been shown to induce apoptosis in certain types of fungi, further enhancing their antifungal activity (Al Aboody and Mickymaray, 2020). In addition, coumarin derivatives exhibit antifungal properties against several plant pathogens, including *Sclerotinia sclerotiorum*, *Phytophthora capsici*, *Fusarium graminearum*, *Botrytis cinerea*, and *Rhizoctonia solani*. The coumarin-derived compounds osthole, imperatorin, psoralen, and ostruthin demonstrate significant antifungal activity (Luo et al., 2022).

6.5. Antiviral activity

Coumarins exhibit antiviral activity due to several factors, including the following:

i) They can inhibit viral replication by binding to specific sites on the virus, thereby preventing it from replicating.

ii) Coumarins can also interfere with the ability of viruses to attach to host cells, which reduces their infectivity.

Iii) Furthermore, coumarins may block certain enzymes involved in viral replication, potentially limiting the spread of the virus within an infected organism or cell culture system (Ali et al., 2021).

iv) Coumarins also stimulate the immune response against viruses, enhancing the body's ability to combat infections more effectively. According to the scientific reports, coumarins such as inophyllum A and inophyllum B exhibit anti-HIV properties. In the literature, coumarins are known for their anti-cancer effects (Hussain et al., 2019). Cytotoxic activity has been identified in isolated, non-substituted coumarin derived from Cassia leaf oil. Imperatorin and other coumarin-based compounds have exhibited anticancer properties (Jebir and Mustafa, 2022). Osthole is effective against breast cancer cells, and esculetin has demonstrated anticancer properties (Chen et al., 2022). Grandivittin exhibited only moderate cytotoxic effects on the A549 cancer cell line. An innovative structural analog of chartreusin, 3″-demethylchartreusin, was isolated from *Streptomyces chartreusis* (Badalamenti et al., 2023).

6.6. Antioxidant activity

Coumarins are compounds known for their antioxidant activity, as they contain phenolic groups that can act as free radical scavengers, thereby reducing oxidative stress in cells. From structural point of view, coumarins feature conjugated double bonds, which enable them

to absorb ultraviolet radiation and protect against DNA damage caused by UV light exposure. The hydroxyl group present in coumarin molecules can donate hydrogen atoms to ROS, such as superoxide anions, thus diminishing their reactivity and preventing cellular damage associated with ROS-mediated oxidation reactions. Furthermore, coumarins exhibit anti-inflammatory activities (Leal et al., 2024), that aid inflammation reducton associated with several diseases or conditions such as diabetes (Niknejad et al., 2024) or cancer (Yadav et al., 2024). Several coumarin-derived compounds, including esculetin, fraxin, grandivittin, and osthol, have exhibited free radical scavenging activity and have been shown to protect cells from oxidative stress (Flores-Morales et al., 2023).

6.7. Antitubercular activity

The antitubercular activity of coumarins has been extensively studied in recent years. Coumarins are a class of compounds that have demonstrated potential as treatments for tuberculosis (Gupta et al., 2023). Studies have found that certain coumarin derivatives can effectively inhibit key enzymes involved in the replication and survival of tuberculosis (TB), such as DNA gyrase and topoisomerases I and II andtheir anti-inflammatory properties may help reduce the inflammation caused by TB infection (Akki et al., 2022). Numerous studies have demonstrated that various coumarin derivatives exhibit anti-inflammatory effects on cells infected with *Mycobacterium tuberculosis*, indicating their potential as adjuvant therapies for the treatment of tuberculosis infections (Fatima et al., 2021; Nibin Joy et al., 2023). Their immunomodulatory activities could potentially enhance immune responses against *M. tuberculosis* infection by activating macrophages and other immune cells responsible for combating bacterial pathogens (Gaio et al., 2023). Phellodenol and umbelliferone, along with the compounds (+)-(S)-marmesin 32, (+)-(S)-rutaretin, and bergapten, were identified in *Fatoua pilosa*. These compounds exhibited varying degrees of efficacy against Mycobacterium tuberculosis at different concentrations (Mujeeb et al., 2022).

6.7. Advances in research on coumarin applications

Previous research on the natural sources of coumarins and their derivatives, which are relevant to their health-promoting qualities (Aydın et al., 2024), has established that plants, fungi, and bacteria are important reservoirs of these bioactive compounds (Ghosh et al., 2022). Plant sources, in particular, have been extensively studied and found to yield a significant number of coumarins and their derivatives, which exhibit diverse pharmacological activities (Tsivileva et al., 2022). Studies have reported that coumarins and their derivatives from natural sources possess various health-promoting properties (Aydın et al., 2024), including antioxidant (Todorov et al., 2023), anti-inflammatory (Leal et al., 2024), anticancer (Mustafa, 2024), antibacterial (Thawabteh et al., 2023), and antifungal activities (Lončar et al., 2023).

These compounds have demonstrated potential in protecting against cardiovascular diseases, neurodegenerative disorders, diabetes, and obesity. Furthermore, they show promising effects on overall health and well-being.

Recent findings have concentrated on the isolation and identification of novel coumarins (Sun et al., 2023), and their derivatives from previously unexplored natural sources. Researchers have been striving to uncover the chemical diversity and biological activities of these compounds. Nowadays, there is a growing interest in understanding the structure-activity relationships of coumarins and their derivatives to optimize their therapeutic potential. Furthermore, recent studies have investigated extraction methods, purification techniques, and formulation strategies to enhance the production and bioavailability of coumarins and their derivatives. This includes the use of innovative approaches such as bioassay-guided fractionation, green extraction techniques, and nanotechnology-based delivery systems. The exploration of natural compounds as potential alternatives to conventional pharmaceuticals has garnered significant attention. Consequently, ongoing research is focused on the safety and toxicity profiles of coumarins (Elmusa and Elmusa) and their derivatives, as well as clinical trials to evaluate their efficacy and therapeutic applications in humans (Sharifi-Rad et al., 2021). Overall, both previous and recent findings underscore the importance of natural sources of coumarins and their derivatives in promoting human health. Ongoing research in this field holds significant promise for the development of novel therapeutics and interventions aimed at enhancing human well-being

7. Future trends and perspectives on natural sources of coumarins and their derivatives

Traditional medicinal herbs and wild species may possess untapped potential; therefore, researchers should continue to investigate lesser-known plant sources that are rich in coumarins. On the other hand, exploring underutilized plant parts—such as roots, stems, and leaves—could uncover new sources of coumarins. Despite their promising biological activities, comprehensive bioavailability data for coumarins is currently lacking. To address this gap, future research must focus on understanding their absorption, distribution, metabolism, and excretion. Bioavailability studies will inform the development of effective formulations and dosages for therapeutic applications. Furthermore, investigating potential synergies between coumarins and other bioactive compounds—such as flavonoids, terpenes, and polyphenols—found in the same plant sources is essential. Combinations of these natural compounds may enhance overall health benefits. Rigorous safety assessments are crucial for coumarin-rich products, necessitating the evaluation of toxicity, interactions, and adverse effects. Regulatory bodies should establish safety standards and guidelines for supplements, foods, and cosmetics that contain coumarins.

Exploring the potential of coumarins in preventing and managing chronic diseases, including cardiovascular disorders, neurodegenerative conditions, and cancer, is a

promising avenue of research. Additionally, researchers should investigate the role of coumarins in modulating immune responses and inflammation. In-depth studies on coumarin pharmacokinetics (the processing of coumarins in the body) and pharmacodynamics (the effects of coumarins) will enhance our understanding of these compounds. Factors such as metabolism, tissue distribution, and target receptors must be considered. Furthermore, the development of eco-friendly techniques for extracting coumarins from plant sources using sustainable methods and green solvents is becoming increasingly important. Investigating individual variations in coumarin metabolism and response will enable personalized approaches to optimize therapeutic outcomes. Formulating functional foods and nutraceuticals enriched with coumarins can contribute to overall health and wellness. Finally, fostering collaboration among botanists, pharmacologists, chemists, and clinicians is essential to advancing coumarin research. Interdisciplinary efforts can lead to innovative discoveries in this exciting field.

Conflict of interest

The authors declare that there is no conflict of interest.

Author contribution statement

Conceptualization and literature search were performed by Nadia Sharif. Hina Jabeen critically analyzed and gave suggestions to finalize the manuscript. All authors read and approved the final manuscript.

Abbreviations

AIDS: Acquired immunodeficiency syndrome; **COX-2:** cyclooxygenase-2; **DVT:** Deep vein thrombosis; **FDA:** Food and Drug administration; **GST:** Glutathione S-transferase; **HIV:** Human immunodeficiency virus; **HLA:** Human leucocyte antigen; **IL-1:** Interleukin-1; **INR:** International Normalized Ratio; **LOX:** Lipoxygenase; **NOS:** Nitric oxide synthase; **PE:** Pulmonary embolism; **PSA:** Prostate-specific antigen; **ROS:** Reactive oxygen species; **TB:** Tuberclosis; **TNF:** Tumor necrosis factor; **UDP:** Uridine diphosphate.

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