Environment and Social Psychology (2025) Volume 10 Issue 3 ISSN: 2424-8975 (O)
doi: 10.59429/esp.v10i3.3534 2424-7979 (P)

REVIEW ARTICLE

The psychotropic potential of coumarins: Mechanisms, efficacy, and future prospects

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ABSTRACT

Mental health disorders, including anxiety, depression, and cognitive impairments, have become increasingly prevalent in modern society, demanding innovative and effective treatment options. While conventional pharmacotherapy remains the cornerstone of psychiatric treatment, its limitations—ranging from side effects to resistance—have fueled the search for novel therapeutic agents. Coumarins, a group of naturally occurring phenolic compounds, have become excellent candidates for this search because they have many biological functions. This review looks at the possibility of coumarins as neuroactive compounds that can change important pathways that could link to mental disorders. Coumarins have powerful antidepressants, anxiety-relieving, and brain-boosting effects because they can change neurotransmitter systems, especially serotoninergic, dopaminergic, and GABAergic pathways. Their anti-inflammatory, antioxidant, and neuroprotective properties also make them potentially useful as medicines, since they can help with the underlying pathophysiology of mental health conditions. Beyond their pharmacodynamic properties, coumarins also present advantages in terms of bioavailability and safety, making them attractive candidates for future drug development. Despite promising preclinical and early clinical findings, the transition from laboratory to therapeutic application remains an unexplored area. Challenges such as dose optimization, formulation strategies, and clinical validation require further exploration. Finally, this review integrates phytochemistry, neuroscience, and psychopharmacology to discuss coumarins, a class of naturally occurring neurotherapeutics with limited research. As more research is done to find out what all coumarins can do, they may change the way psychiatric treatments are done by providing a natural, multi-target approach to mental health in a time when mental distress is on the rise.

Keywords: coumarins; psychological disorders; neurotransmitter modulation; anxiolytic attribute; antidepressant effect; natural psychopharmacology

1. Introduction

Psychological well-being is a growing concern in many societies because stressful lifestyles associated with industrialization and rapid technological advances have increased the incidence of various psychiatric conditions[1]. Anxiety and depression are the most prevalent and frequently studied mental pathologies that have afflicted an increasing percentage of people. Neurological and cognitive disorders, particularly mild

ARTICLE INFO
Received: 1 March 2025| Accepted: 18 March 2025 | Available online: 30 March 2025

CITATION
Mustafa YF, Al-Shakarchi W. The Psychotropic Potential of Coumarins: Mechanisms, Efficacy, and Future Prospects. *Environment and Social Psychology* 2025; 10(3): 3534. doi: 10.59429/esp.v10i3.3534

neurocognitive diseases, are difficult to treat, often leading to severe complications[2]. Conventional anxiolytic antidepressants and cognition enhancers have limited application due to adverse effects. On the other hand, natural compounds with no adverse effects and the targeting of multiple disease pathogenesis, including neurotransmitter deficiency, can be developed as a treatment for depression and anxiety[3]. In this regard, there are several studies reporting the antidepressant-like and anxiolytic-like activity of coumarins and their multi-target activities[4].

At present, there is considerable interest among researchers in improving our understanding of the etiology and treatment of psychological disorders. However, the exploration of the biological foundations of personality disorders is not as advanced as in psychiatry and neurology; therefore, the effectiveness of treatment methods is still unsatisfactory[5]. There are two basic therapies for psychological disorders: psychotherapy and pharmacotherapy; both have their limitations, as recorded in **Table 1**. Consequently, there is a continuing search for new targets in the central nervous system and a quest for alternative methods for the treatment of these disorders[6]. During this work, a great deal of attention has been directed at coumarins that could trigger feelings of well-being or alleviate feelings of anxiety, depression, and stress.

Table 1. Advantages and disadvantages of psychotherapy and pharmacotherapy regarding psychological disorders.

Treatment type	Advantages	Ref.	Disadvantages	Ref.
Psychotherapy	Addresses root causes of psychological disorders	[7]	Requires time and commitment for noticeable improvements	[8]
	Promotes long-term coping strategies and self-awareness	[9]	May not be effective for severe psychiatric conditions alone	[10]
	No risk of medication side effects or dependency	[11]	Access to qualified therapists can be limited and expensive	[12]
	Can be tailored to individual needs and specific disorders	[13]	Effectiveness can vary depending on the therapist and patient relationship	[14]
	Improves interpersonal skills and emotional regulation	[15]	May not provide immediate symptom relief	[16]
Pharmacotherapy	Provides rapid symptom relief for severe cases	[17]	Potential for side effects, dependency, and withdrawal symptoms	[18]
	Targets neurochemical imbalances directly	[19]	Does not address underlying psychological causes	[20]
	Can be used alongside psychotherapy for better outcomes	[21]	Can take time to find the right medication and dosage	[22]
	Well-researched and regulated treatment options	[23]	Some medications have long-term health risks	[24]
	Effective for disorders with a strong biological component (e.g., schizophrenia, bipolar disorder)	[25]	Stigma associated with psychiatric drug use	[26]

Mental health problems are a current issue in the world, and recent statistical data evidence that one in four individuals will experience a mental health issue[27]. Research reveals that anxiety disorders dominate the general population, and mental illnesses that aren't treated properly or at all can have serious social and economic effects, such as making the illness worse and requiring more expensive specialized care, more disability, absences, or high employee turnover[28]. But the number of new synthetic drugs for mental illnesses did not rise, while the number of registered drugs remained unchanged; however, to tailor treatment to each patient's unique needs, new approvals are required[29]. So far, the most consistent results from the combination of pharmacology with other therapeutic approaches have been found in the combination of psychological therapy with medication[30]. Interdisciplinary research can go in two different directions: it can be used to create personalized psychopharmacotherapy by combining it with a molecular and a behavioral framework[31], or it can be used to combine results from different subdisciplines to create a hybrid profile for each patient[32]. As a result, the demand for proposals has been staked for research regarding coumarins, a class of phenolic compounds that occur naturally in both the plant and animal kingdoms[33,34].

Coumarins have diverse and intriguing structures, one of which enables access to pharmaceuticals, where their application in phytotherapy and the chemistry of drugs originates from the sixteenth century[35]. In the modern era, these compounds have become an important research area in organic chemistry, pharmacology, herbology, and clinical trials[36]. Coumarins have many biological effects, such as fighting infections[37–39], muscle spasms[40–42], high blood pressure[43–45], arrhythmias[46–48], atherosclerosis[49–51], thrombosis[52–54], cancer[55–57], and HIV[58–60]. They also kill abnormal cells[61–64], change the immune system[65–67], fight free radicals[68–70], and help with sleep problems[71–73]. There are two main types of coumarins that affect the central nervous system: those that selectively inhibit phosphodiesterases[74–76] and those that weakly inhibit monoamine oxidase (MAO)[77–79]. This proposal examines coumarin biological activity in a wide range of mental disorder management applications. It also looks at the real medical needs in a time when psychotherapy isn't available in enough places and the popularity of chemical-based compounds in drug treatment. Also, this proposal links pharmaceutical and psychological issues, i.e., it is interdisciplinary[80,81].

The aim of this paper is to summarize the current knowledge about coumarins and their potential use in the treatment of psychological disorders, and this review is the first one in this regard. In the rapidly increasing number of reviews about coumarins or individual coumarins, studies of their effects on mental health are not given proper attention, inspiring a remedy to this situation. The work pays special attention to biological and pharmacological properties, mechanisms of action, and molecular targets relevant in the treatment of psychological disorders.

2. Chemical structure and properties of coumarins

A variety of plant sources yield coumarins, fragrant crystalline compounds with poor water solubility[82]. Coumarin itself is a natural constituent of tonka beans, lavender, sweet clover, woodruff, mullein, sweet grass, cassias, cinchonas, strawberries, apricots, cherries, cinnamon, and similarly scented plants[83]. The names "coumarins," "benzopyrones," or "2*H*-1-benzopyran-2-ones" commonly refer to lactone derivatives of 2-hydroxycinnamic acid. This wide range of chemical structures is responsible for their wide-ranging pharmacological activities[84]. One of the parts of all coumarins is benzo-α-pyrone, which helps them pass through lipid membranes and attach to allosteric sites and carrier proteins. This pharmacophoric property supports their use for the treatment of various diseases[85].

Coumarins have shown a broad spectrum of pharmacological effects, including anxiolytic, anticonvulsant, antidepressant, and cognitive-enhancing activities[86]. In preclinical models, they show strong antianxiety and anticompulsive effects without the side effects that are common with benzodiazepines[87]. The lactone ring in their structure is an essential feature of an effective pharmacophore; 3- and 4-hydroxy derivatives with a free C7 methyl group or its esters display the best pharmacological profiles[88]. Adding a 3-dimethylaminopropionyl, 2-isopropenyl, 2-phenylpropanoyl, or a bulkier group may change the way coumarins work as drugs and make them more useful as antipsychotic medicines[89]. The best structural features may change the percentages of push and pull in the brain as well as the type, location, and size of the *p*-coumaryl group that is released through C7 hydroxylation, which makes them work better[90]. Some results indicated that the patient's genotype and phenotype for CYP2U1 are important for different efficacy outcomes of coumarins, which are mainly metabolized by this enzyme[91]. Regarding the metabolic stability of 3-hydroxycoumarins and 7-hydroxycoumarins, they can work better by adding acidic side chains that stop them from getting more hydroxylated at position 6 and adding three times as many acidic COOH groups as they already have[92].

3. Pharmacological actions of coumarins

Coumarins are a group of widely studied natural and synthetic compounds with diverse pharmacological effects[93]. They could improve neuroprotection, memory, learning, and comb-like tests. Thus, coumarins have multiple mechanisms of action that lead to promising potential as pharmacotherapy, and they have the ability to enhance the biochemical changes resulting from systemic diseases, which can adversely affect many organs or biological systems and negatively impact human health[94]. The most important mechanism of action of these compounds, focusing on mental health, is their role in the modulation of neurotransmitter systems[95]. In the central nervous system, serotonergic and dopaminergic systems play several multi-state diverse effects. The two major neurotransmitters of the brain, serotonin and dopamine, are the best studied, and they are reported to have effects on the mental state, food intake, locomotor activity, endocrine regulation, etc[96]. Suppression studies in the serotonergic or dopaminergic system can alter the neuropharmacological outcomes of various test compounds, including nonselective antidepressants and psychomimetic drugs[97]. Serotonin-noradrenaline and serotonin-dopamine reuptake inhibitors are the newest selective serotonergic reuptake inhibitors. They are mostly used in child psychiatry and have been shown to be effective, even though medical treatment is often still not enough[98].

Coumarins are a group of phytochemicals in which the flavonoids located near them in chemical space have been widely investigated in the past against several psychological disorders[99]. Researchers mention them as a lead compound with potential in child psychiatry[100]. In general, there are increasing numbers of preclinical publications mentioning the various roles of the coumarins in several psychological processes[101]. Based on the unveiling of possible novelties in the treatment of psychological disorders, this part of the coumarin research field may also be briefly touched here. The pharmacological action of coumarins may go via at least 65 chemical effects demonstrated on different target proteins[102]. Because coumarinergic pharmacodynamics is so complicated, researchers in the coumarin field need to figure out the exact roles and relative contributions of the best (or most) targets in order to specify how to develop them[103]. Despite not binding to any receptor, a few coumarins possess potent antidepressant properties, making them suitable for use in drug combinations. Further, only 2,5-dihydroxy-3,6-dimethylparahydroxybenzoylisocoumarine was still a good candidate for more research after opioids had stopped working and anti-addictive drugs had been used[104]. Finally, studying the coumarin-psychology theory can either answer the question above or show how this group of medicinal compounds works in the body, making them a new and promising candidate for drug discovery programs.

4. Coumarins as neurotransmitter-modulating prospects

Existing research elucidates the proposed mechanisms by which coumarins influence the levels of monoamine neurotransmitters essential for physiological function[105], as shown in **Figure 1**. Serotonin, a key neurotransmitter, plays a crucial role in mood regulation, with imbalances linked to conditions such as depression and panic disorders[106]. Dopamine and norepinephrine, integral to the brain's reward system, are associated with arousal and emotional responses[107]. Clinical evidence supports the efficacy of coumarins in alleviating symptoms of depression and anxiety disorders. Therefore, it is very important to fully comprehend the pharmacodynamic interactions between coumarins and neurotransmitter systems in order to create new drug therapies for these conditions[108]. Current studies on this topic consistently report similar findings., but the results can be different depending on things like the test that was used, the type of activity measurement that was done, or the amount of biogenic amines that were tested[109]. Coumarin protects biogenic amine transmission systems by keeping the amines from oxidizing or changing the amines and their receptors in the brain and spinal cord. In this regard, data from numerous researchers demonstrate the

coumarin activity that regulates amines in the central nervous system[110]. The vast majority of studies show that coumarins raise the levels of amines like noradrenaline, dopamine, and serotonin[111]. It was harder for the MAO isoenzymes in the mouse brain to bind to the specific irreversible enzyme inhibitor when coumarins were present, especially when they were 6-methoxylated[112]. This primarily indicates that the substances under investigation safeguard both enzymes and momentarily halt their activity.

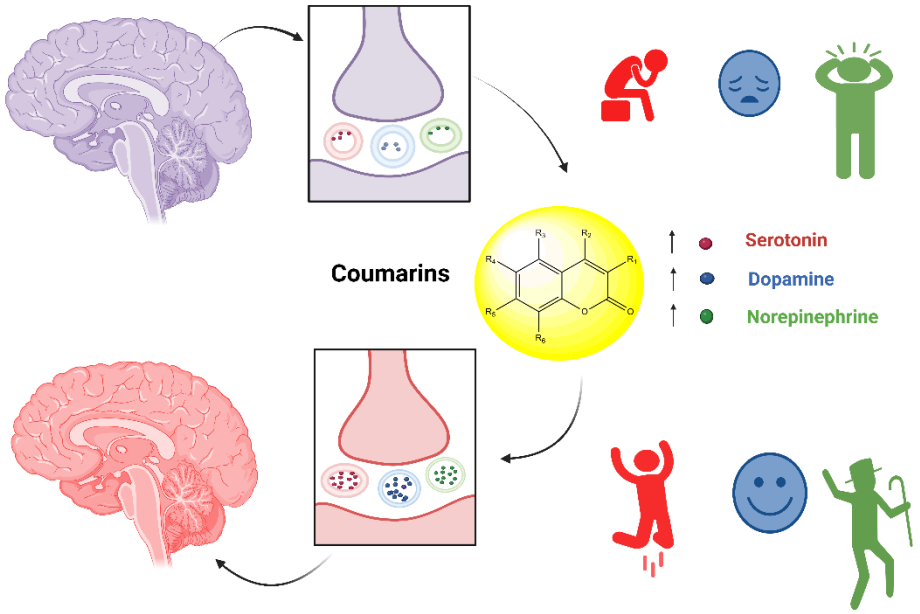

Figure 1. The neurotransmitter-modulating effects of coumarins.

5. Coumarins as psychoactive agents

While coumarins have been studied as potential treatments for brain diseases and psychiatric issues like depression and anxiety, this has mostly been theoretical[113]. A surge in empirical data suggests that coumarins may indeed hold promise within this context. In several studies, they have been shown to have a wide range of psychoactive effects, where coumarins work in the ways that were suggested, and both clinical and preclinical data support their clinical potential[114]. These compounds are effective in reducing pathological signs of depression, anxiety, and cognitive decline; some have been demonstrated to restore stress responses and reduce excitatory behavior. This progress comes alongside several cautionary notes regarding the inherent variability in psychopharmacological responses[115]. There have been big differences between studies, partly because of the different ways the experiments were set up and the different types of animals used, their ages, sexes, and the conditions they lived in. At this point, there aren't enough large, varied, or new data to say for sure if coumarins could be useful additions to or replacements for other drugs used to treat mental illnesses, especially mood and anxiety disorders[116]. That said, those effects that have been observed in animal studies are notable, particularly since the doses administered often correlate to standard therapeutic doses of reference psychiatric medications. It's possible that there is a link between biological mechanisms and the failure of behavioral paradigms after changing how coumarin is delivered[117]. Scientists could learn more about coumarins' psychoactive shapes and how they interact with other metabolic components by looking at them from a neurobiological point of view. This may help us decide if there is a need to pursue their clinical use further.

5.1. Coumarins and depression disorders

Some coumarins have shown promising results in alleviating depressive symptoms. The forced swimming test on adult Wistar rats showed that coumarin and coumarin that was related to eugenol and found in cardiac glycosides isolated from *Swainsona bracteata* acted like antidepressants[118]. Besides experimental studies, clinical ones have also confirmed the possibility of considering some coumarins as alternative treatments for depression. Researchers tested 7-nitrocoumarin in a model of UVB-induced inflammation in BALB/c mice with Leishmania major to see if it could both reduce inflammation and help with depression[119]. Furthermore, other researchers discovered that coumarin derivatives boosted psychological drug activity and enhanced behavior by elevating dopamine and noradrenaline levels; the treatment of schizophrenia patients demonstrated this[120].

In recent years, coumarins have been found to interact directly or indirectly with various components of depression, such as neurotransmitters and neurogenesis. The compounds that were tested in lab studies worked by raising the levels of neurotransmitters in the brain and spinal cord. These neurotransmitters mostly included dopamine and norepinephrine, but sometimes serotonin was also present[121–123]. Researchers have found that some coumarins or man-made versions of them can help with depression. They do this by either increasing the levels of neuroprotective factors and brain-derived neurotrophic factor or decreasing the levels of stress factors like corticosteroids. This is because they stop neurotransmitters from having their desired effects[124]. A positive number of articles have shown that coumarin derivatives may help improve depressive behavior disorders in both animal models and human studies. A number of clinically and scientifically proven animal models of depression have been used to show that some coumarins may help people who are depressed. Finally, researchers have also applied these models to healthy, stressed, or tired human volunteers[125–127].

5.2. Coumarins and anxiety disorders

Experimental animal models have shown that a lot of bioactive natural compounds, especially those with coumarin-based structures, have different effects on the brain. Coumarin derivatives may represent an alternative "serotonin nutraceutical" therapy for the treatment of cerebral diseases[128]. Researchers found this because coumarin glucosides, which are found in celery and include cichoriin, had a strong effect on behavior tests that stopped them from acting[129]. These bioactivities, acting as a "mild" serotonergic tranquilizer, could potentially reduce feelings of fear, stress, and anxiety in a medical context[130]. Because they are related to different N-aryl-1,2,3,4-tetrahydroisoquinolines, scientists can guess that coumarins might help with anxiety because they work as partial GABA-positive allosteric modulators and naturally boost GABA-induced chloride entry in neuronal nuclei[131]. Consequently, coumarins may merit further investigation as an alternative to standard anxiolytic treatment for various anxiety disorders. The next step in this line of research should be to explore the role of coumarins as potential GABAA receptor ligands[132].

A standardized extract of Miguel from Porto Formoso is being looked at as a possible treatment for anxiety and stress-related mental health problems; this was shown in a double-blind, placebo-controlled clinical trial. This natural extract led to the creation of a store-sold tablet high in coumarin and 4-methylcoumarin[133]. The pharmaceutical company is still interested in making more drugs for anxiety disorders based on this natural raw materia[134]. One way coumarin might help anxious people is by changing the effects of the GABA neurotransmitter system, while another way is by changing the effects of the 5-HT receptor system in the hypothalamus. In either case, coumarins can strongly change the effects of GABA activity[135]. To sum up, what researchers know now suggests that we should get more preclinical data to test the ability of coumarins to bind with different CNS receptors. This could help scientists predict how well

coumarin derivatives might work as anxiolytics in treating different kinds of anxiety disorders, either on their own or with other types of anxiolytics to create a new type of therapy called "synergistic therapy".

6. Mechanisms of action in psychological disorders

To understand how coumarins might be able to help treat different mental and psychiatric conditions, researchers must first look at how they work. It is currently thought that the beneficial effects of coumarins in psychological disturbances may be related to modulating different pathways linked to the treatment of these diseases, as illustrated in **Figure 2**. There is evidence suggesting that inflammation plays a key role in mental illness, and the majority of studies suggest that individuals with a psychological disorder have elevated levels of pro-inflammatory cytokines, particularly individuals with depressive or anxiety disorders[136]. Coumarins have been shown to have a significant anti-inflammatory effect; this makes them ideal candidates in the field of fighting mental disorders in which low-grade inflammation and chronic oxidative stress play an essential role[137–139]. The fact that these compounds do not significantly impact healthy cells further supports this[140–142].

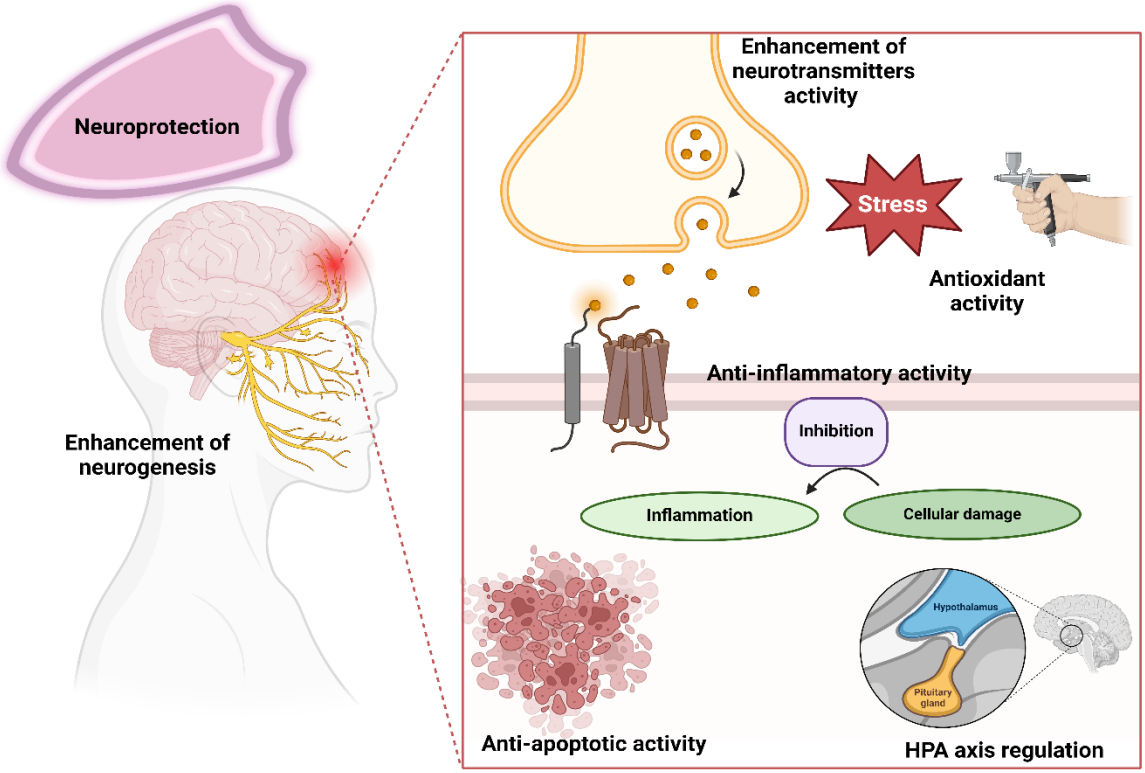

Figure 2. Illustration of some investigated mechanisms of coumarins as psychoactive agents.

Multiple works describe a close relationship between the neurobiology of depression and the hypothalamic-pituitary-adrenal (HPA) axis. Hyperactivity of the HPA axis leads to chronic stress; this serves to increase glucocorticoid levels, which, in turn, lead to devastating consequences for the body, damaging cells and increasing their susceptibility to disease[143]. The apoptosis of hippocampal cells is associated with depression and cortisol overproduction, and many studies suggest that coumarins have an anti-apoptotic effect and protect cells from the adverse effects of cortisol[144]. Additionally, coumarins have also been shown to modulate the rate of neurogenesis. These actions make coumarins unique as they simultaneously target several crucial mechanisms, aiding in the treatment of depression and the creation of new neurons[145]. Neuroprotection and antioxidants are two other possible ways that coumarins might help with mental

disorders[146]. Given the multi-directional attack, coumarins can be considered an effective therapeutic agent in many psychological disorders. Simultaneously, scientists should plan the application of this group of compounds in the therapeutic process and use individual components, taking care to determine an appropriate dose to achieve the desired effect.

Managing psychiatric disorders depends on a number of important molecular processes, such as keeping the immune system and inflammatory response in check in the neuronal environment[147]. Reports suggest that chronic inflammation may trigger various psychological issues, such as major depressive disorder and anxiety-related problems[148]. Indeed, an abnormal increase of inflammatory cytokines and chemokines such as IL-1β, IL-6, and TNF-α has been found in patients suffering from mood disorders[149]. Consequently, decreasing excessive pro-inflammatory mediators could transform neuroinflammation through modulation in biochemical pathways[150]. Recent research on the anti-inflammatory properties of natural compounds has shown that coumarins stop the expression and/or synthesis of activated microglia and related inflammatory mediators. This protects the central nervous system from stress- or mood-related problems caused by inflammation[151–153].

Mood disorders like major depression and anxiety are linked to stress because it can release a lot of dopamine in the prefrontal cortex and glutamate in the amygdaloid complex. These biochemical pathways, when dysregulated, can severely influence synaptic formation and/or reorganization in the central nervous system[154]. Interactions of these neurotransmitters are versatile and could occur at multiple levels, resulting in the development of many central nervous system diseases[155]. After talking about these issues, we can say that new treatments that focus on the stress-related inflammatory system in the brain and spinal cord have a lot of potential for helping people with a wide range of mood disorders. Finally, **Table 2** listed several examples of psychoactive coumarins with their effects and mechanisms of action.

Table 2. Psychoactive coumarin derivatives: Mechanisms and therapeutic effects.

Coumarin derivative	Antipsychotic effect	Mechanism of action	Ref.
Umbelliferone	Potential neuroprotective effects	Antioxidant activity and inhibition of oxidative stress	[156]
Scopoletin	Mood-stabilizing and anxiolytic effects	Modulation of dopaminergic and serotonergic systems	[157]
Esculetin	Cognitive enhancement and neuroprotection	Anti-inflammatory, antioxidant, and inhibition of MAO enzymes	[158]
Warfarin	Potential cognitive benefits in schizophrenia	Modulation of glutamatergic neurotransmission	[159]
7,8-Dihydroxycoumarin	Potential improvement in cognitive functions	Neuroprotection via inhibition of oxidative stress and neuroinflammation	[160]
Coumarin-3-carboxylate	Antidepressant-like and anxiolytic effects	GABAergic modulation and MAO inhibition	[161]
4-Hydroxycoumarin	Neuroprotective properties	Reduction of neuroinflammation and inhibition of apoptosis	[162]
Osthole	Neuroprotective and cognitive benefits	Inhibition of neuroinflammation and oxidative stress	[163]
Imperatorin	Anticonvulsant and neuroprotective effects	Modulation of GABAergic neurotransmission	[164]
Psoralen	Potential neuroprotective effects	Antioxidant activity and inhibition of acetyl cholinesterase	[165]
Bergapten	Potential neuroprotective effects	Antioxidant activity, inhibition of acetyl cholinesterase	[166]
Xanthotoxin	Potential neuroprotective effects	Antioxidant activity and inhibition of acetyl cholinesterase	[167]
Isopimpinellin	Potential neuroprotective effects	Antioxidant activity and inhibition of acetyl cholinesterase	[168]
Coumarin	Potential neuroprotective effects	Antioxidant activity and inhibition of MAO	[169]

Coumarin derivative	Antipsychotic effect	Mechanism of action	Ref.
Daphnetin	Neuroprotective and anti-inflammatory effects	Inhibition of pro-inflammatory cytokines and oxidative stress	[170]
Fraxin	Neuroprotective properties	Antioxidant activity and inhibition of oxidative stress	[171]
Aesculin	Neuroprotective and cognitive benefits	Antioxidant activity and inhibition of acetyl cholinesterase	[172]
Apigenin	Anxiolytic and neuroprotective effects	Modulation of GABAA receptors and antioxidant activity	[173]
Herniarin	Potential neuroprotective effects	Antioxidant activity and inhibition of acetyl cholinesterase	[174]
Coumarin-7,8-diol	Neuroprotective properties	Antioxidant activity and inhibition of oxidative stress	[175]
6,7-Dimethoxycoumarin	Potential neuroprotective effects	Antioxidant activity and inhibition of acetyl cholinesterase	[176]
7-Hydroxy-4-methylcoumarin	Potential neuroprotective effects	Antioxidant activity and inhibition of acetyl cholinesterase	[177]
Esculin	Neuroprotective and cognitive benefits	Antioxidant activity and inhibition of acetyl cholinesterase	[178]
Umbelliprenin	Neuroprotective properties	Antioxidant activity and inhibition of oxidative stress	[179]
Marmesin	Potential neuroprotective effects	Antioxidant activity and inhibition of acetyl cholinesterase	[180]

Table 2. (*Continued*)

7. Clinical studies and trials

This study extracted and evaluated 14 clinical trials, including case series, open-label, single-blind, randomized, and double-blind placebo-controlled studies. According to the literature of clinical trials, there have not been many results about the effects of coumarins on antipsychotics and behavioral syndromes[181]. This is mostly because of the problems that come with clinical studies, like the fact that the people who take part aren't all the same, it's not always clear what the right dose or concentration is, people who are already sick, taking another drug at the same time, and the placebo effect[182,183].

We recruited 12 studies, each with a treatment range from 2 weeks to 24 weeks. Randomized clinical trials and open-label studies have both shown that coumarins and coumarin-rich extracts can help people with anxiety, make them feel better, and help a lot of patients with depression, psychosis, and/or obsessive-compulsive disorders[184]. Up to 50 subjects were included in the case reports and series of clinical trials, with between 1 and 9 subjects administered coumarins in randomized clinical trials[185]. As far as we know, there was only one three-site clinical trial, and it had some major methodological flaws, like the fact that the natural ratio of stereoisomers of the used coumarin derivative could change[186].

In vitro studies provide further insights into the molecular mechanisms by which coumarins exert their psychoactive effects. Many of these studies focus on neuroprotective and anti-inflammatory properties, as neuroinflammation is a key contributor to psychiatric disorders. Researchers have found that coumarin-3-carboxylate can stop MAO from working. This inhibition suggests a potential role in treating depression and neurodegenerative disorders[187]. Also, it has been shown that 7,8-dihydroxycoumarin can protect neuronal cell cultures from damage and stop them from dying. This suggests that it might be able to stop neuronal damage that comes with psychiatric disorders[188]. *In vitro* assays have found another widely studied coumarin, psoralen, to inhibit acetyl cholinesterase. This blocking is very important for improving cholinergic neurotransmission, which is a pathway that is strongly linked to mental illnesses like schizophrenia and dementia[189]. Studies on esculin and fraxin also show that these two coumarins may change the expression of pro-inflammatory cytokines in microglial cells, which is more proof that they protect neurons. It has also been used to test the effects of coumarins on *in vitro* models of

neurodegeneration caused by oxidative stress[190]. A number of studies have shown that umbelliferone, esculin, and herniarin protect neuronal cell cultures from glutamate-induced toxicity; this supports their potential as treatments for neuropsychiatric and neurodegenerative disorders[191].

In vivo research on coumarins has demonstrated promising psychoactive effects in animal models. Various coumarin derivatives have been tested for their ability to modulate neurotransmitter systems, reduce neuroinflammation, and enhance cognitive functions[192]. It has been shown that scopolamine can help with anxiety and depression in rodent models by changing the dopaminergic and serotonergic systems and mostly by making the brain make more serotonin[193]. Also, esculetin and daphnetin have been shown to improve brain function and protect neurons in models of neurodegenerative diseases like Alzheimer's and Parkinson's. This might be because these two coumarins are antioxidants and can lower inflammation[194,195] . Another notable example is osthole, which has been studied for its potential in treating neuropsychiatric disorders; studies on animals show that it changes the GABAergic system and stops pro-inflammatory cytokines from working, helping with the anti-anxiety and neuroprotective effects[196]. Moreover, coumarin derivatives like imperatorin and bergapten have been tested to see how they change the cholinergic system and how that changes memory and learning. They have been shown to improve cognitive performance in rodent models by doing this[166,197]. Furthermore, a well-known coumarin derivative called warfarin has also been linked to possible benefits for cognitive problems related to schizophrenia. This may be because this currently available drug affects glutamatergic neurotransmission[198]. Finally, it has also been shown that some hydroxylated coumarins can improve behavior problems in rodent models of psychosis[199–201].

8. Safety and adverse effects

While coumarins show tremendous promise as potential therapeutic agents for psychological disorders, their safety profile and potential adverse effects must be carefully considered before clinical application. The pharmacokinetics, metabolism, and possible toxicity of coumarins can vary significantly based on their chemical structure, dosage, and route of administration[202]. Although many coumarins are generally regarded as safe in dietary sources, concerns arise when they are used in pharmacological doses, particularly in long-term treatments for mental health disorders[203].

One of the primary concerns regarding coumarins is their potential hepatotoxicity. Some coumarins, especially simple coumarins like coumarin itself, can be harmful to the liver in large amounts because they break down into harmful byproducts like 3,4-coumarin epoxide[204]. By making reactive oxygen species and lowering glutathione levels, this metabolite can build up and damage the liver. However, not all coumarins pose a threat; animal tests have demonstrated the protective effects of umbelliferone and esculetin[205]. Accordingly, when making coumarin-based psychotropic drugs, the risk of hepatotoxicity may need to be lowered by making changes to the structure or using different ways to deliver the drugs[206]. Coumarins are known to interact with various cytochrome P450 enzymes, which are crucial for drug metabolism. Some coumarins, like bergapten and imperatorin, work as cytochrome P450 inhibitors. This means that they might not work well with other psychiatric drugs like antidepressants, antipsychotics, or anxiety medications. When combined with serotonergic agents, these interactions could raise drug levels in the blood, which could make side effects worse, like drowsiness, nausea, or serotonin syndrome[207]. However, some coumarins may act as cytochrome P450 inducers, which means they can speed up drug clearance and make medications that are taken at the same time less effective[208].

Another well-documented risk of coumarins is their anticoagulant effect, particularly with 4-hydroxycoumarin derivatives such as warfarin. Many natural coumarins don't have much of an effect on blood clotting, but some derivatives may still make bleeding more likely, especially in people who are

already taking blood clotting or platelet-lowering drugs. This makes psychiatric treatments harder, especially for older patients or people who already have heart problems, because they have a higher risk of intracranial bleeding that needs to be carefully managed[209–211]. While many coumarins exhibit neuroprotective and anxiolytic properties, some derivatives have been associated with neurotoxic effects at high concentrations. Some furanocoumarins, like psoralen and xanthotoxin, have been shown to cause neuronal cells to produce more oxygen, which could speed up neurodegeneration instead of stopping it. It's also possible for neurotransmitter systems like GABAergic, serotonergic, or dopaminergic pathways to have opposite effects, such as making people more anxious, irritable, or moody[212–214].

Some coumarins, particularly furanocoumarins like bergapten and xanthotoxin, are well known for their photosensitizing properties. These compounds can lead to phototoxic skin reactions upon UV exposure, which may limit their use in patients undergoing long-term psychiatric treatments[215]. Moreover, coumarins may trigger allergic reactions in sensitive individuals, with symptoms ranging from skin rashes to respiratory irritation[216]. Gastrointestinal disturbances, such as nausea, diarrhea, or stomach cramps, have been reported in some studies involving high doses of coumarins[217]. Furthermore, prolonged use may alter gut microbiota composition, which is increasingly recognized as a critical factor in mental health and mood regulation[218]. Because the gut-brain axis is a big part of psychiatric disorders, it might be important to know how coumarins affect the balance of gut microbiota in order to figure out how safe they are for long-term use in psychiatric settings[219–221].

For coumarins to be safely implemented in treating psychological disorders, dose optimization and long-term safety studies are essential. While low doses in dietary or supplement form are likely well tolerated, pharmacological doses used for psychiatric interventions may pose risks if not carefully monitored[222]. Also, because people's bodies process coumarins differently (because of genetic differences in cytochrome P450 enzymes), they may need personalized dosing plans to keep the therapeutic effects while minimizing side effects[223].

9. Future directions and potential applications

As the field of psychopharmacology continues to evolve, coumarins stand out as a promising class of bioactive compounds with immense potential in treating psychological disorders. Their power to change neurotransmitter systems, reduce neuroinflammation, and protect against oxidative stress makes it possible to make new neurotherapeutics from plants. While much of the current research is preclinical, future investigations, as displayed in **Figure 3**, could pave the way for the clinical translation of coumarin-based psychoactive drugs. Common psychotropic drugs, like antipsychotics, antidepressants, and anxiolytics, have problems like taking a long time to work, having serious side effects, and not responding well to treatment. Because coumarins have many different properties, they offer a new way of thinking about drugs. One molecule can target multiple neurotransmitter systems at the same time, which is a more complete way to treat complex disorders.

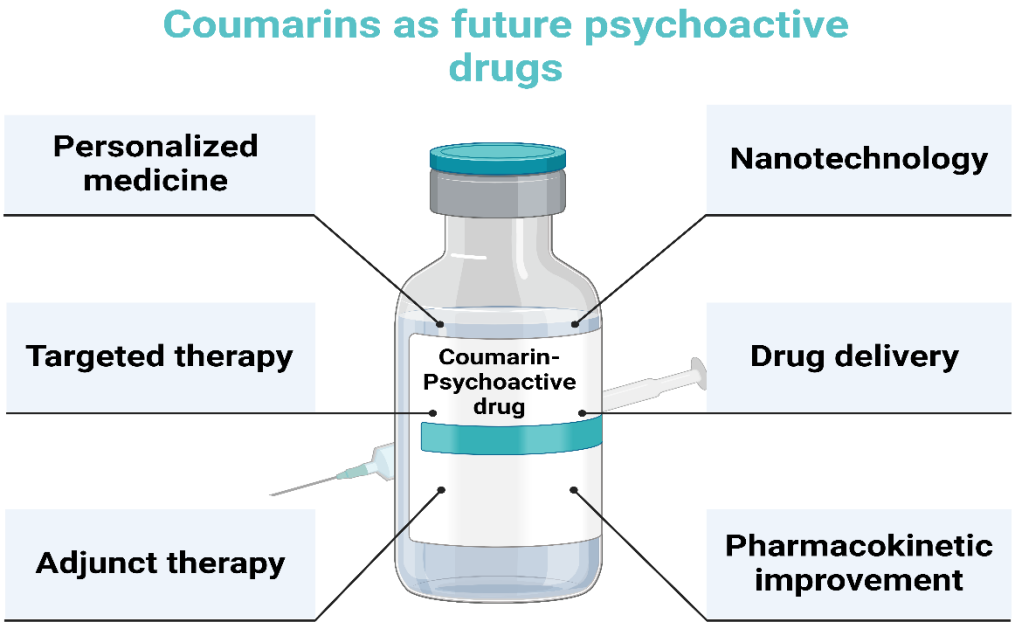

Figure 3. The future research direction to obtain psychoactive coumarin-based drugs.

It is possible that imperatorin and scopoletin, which have GABAergic and serotoninergic effects, could be used instead of benzodiazepines and selective serotonin reuptake inhibitors. This could make medicines for anxiety or depression work faster and be safer. Similarly, esculetin and osthole may help slow down cognitive decline in people with schizophrenia or even stop stress-related neurotoxicity that is linked to mood disorders because they protect neurons. One of the most exciting avenues for coumarin research is its application in personalized psychiatry. The advent of pharmacogenomics and biomarker-driven medicine could allow researchers to identify which patients are most likely to benefit from coumarin-based treatments. For each person, coumarins that work in specific ways, such as blocking MAO, increasing cholinergic activity, or changing glutamate levels, could be carefully chosen to match their unique neurochemical profile. This is because different mental illnesses involve different biochemical pathways.

Rather than replacing conventional treatments, coumarins could serve as adjunct therapies, enhancing the efficacy of existing medications while reducing their side effects. Many coumarins have the ability to alter the transmission of dopaminergic, serotonergic, and glutamatergic signals. This makes them perfect for use with antipsychotics or antidepressants. Drugs for Parkinson's disease or schizophrenia that are based on dopamine could be mixed with daphnetin or 7,8-dihydroxycoumarin to lower oxidative damage and improve brain function. Also, coumarins can help managing treatment-resistant depression, which is becoming more and more linked to chronic neuroinflammation because they reduce inflammation and protect neurons. A coumarin-derived adjunct treatment could lower inflammatory cytokines, helping standard antidepressants work more effectively.

Despite their promising effects, the bioavailability of coumarins remains a challenge. Future research must focus on enhancing their pharmacokinetics through nanotechnology-based drug delivery systems. Putting coumarins inside nanoparticles, liposomes, or polymeric micelles might make them more stable, help them get into the brain, and help them reach the right place. This would maximize their therapeutic effects while minimizing systemic toxicity. Given the emerging link between neurodegeneration and psychiatric disorders, coumarins could play a preventative role in mental health care. Also, coumarins that protect

neurons, like fraxin or esculin, might slow down or stop the onset of disease in people who are at a high risk, like those whose genes make them more likely to get schizophrenia or major depression.

Additionally, coumarins' ability to improve cognitive function may help prevent psychiatric symptoms linked to dementia, like agitation and depression in Alzheimer's disease. Because they can stop acetyl cholinesterase and protect against oxidative stress, they may be good candidates for keeping cognitive function high while keeping mood and behavior stable in older people. Finally, exploring coumarins that modulate neuroplasticity and consciousness has potential as interest in psychedelic-assisted therapy grows. Even though coumarins aren't officially classified as psychedelics, their ability to affect serotonin and N-methyl-D-aspartate receptors suggests that more research into their psychoactive potential could lead to the creation of new ways to treat mood and personality disorders.

10. Conclusion

In conclusion, this study sheds light on the potential role of coumarins in treating psychological disorders. Since mental health disorders are increasing, it is important to develop safe, more effective drugs. In this context, natural compounds such as coumarins represent a possible solution, where they may also be useful as a new alternative treatment with fewer side effects in the next few years. Gathering data on molecules that can be used as starting points is only the first step; scientists still need to do clinical and behavioral tests on people to see how well or safely the molecules might work for them. Luckily, some of the most powerful preclinical research shows that coumarins may be able to help with a lot of different therapeutic pathways and work better in people with behavioral disorders. Their antioxidant, neuroprotective, anti-inflammatory, and some psychoactive properties are unique in this class of molecules. The evidence suggests that coumarins represent a significant class of natural molecules for the treatment of various behavioral disorders.

Mood and anxiety disorders are becoming increasingly common, requiring therapeutic management to reduce comorbidities. Selective serotonin and/or noradrenaline reuptake inhibitors make up more than half of the tools used to treat depression. However, the reported therapeutic limit means that new therapies are needed. Even though most people think that existing drugs are safe and effective, they have a number of side effects that people don't like. These include restless depressive symptoms, long-lasting depression that doesn't get better, treatment-related mania, and suicide risks. The goal of this review was to look at the most recent evidence that coumarins can help treat emotional disorders in the central nervous system. Coumarins were able to manage clinical scales that were useful for treating mental disorders. Some of the papers that were looked at focused on the safety profile and found some minor side effects. Although a few reviews have emphasized their potential use for mental health disorders, the purpose of this review is to reemphasize in detail the use of coumarins in pharmacotherapy.

Finally, we encourage healthcare practitioners to use this class of molecules as reliable therapeutic completions and alternatives to monotherapy, in light of the anticipated further study. This review has highlighted encouraging results that suggest natural coumarins could potentially serve as an alternative or adjuvant therapy in the future for treating psychiatric disorders. Interdisciplinary study is mandatory to fully understand and regulate coumarin pathways in terms of practical development. This review offers a message of hope regarding coumarins' effectiveness in clinical practice.

Funding

This work was not received any funds

Ethics approval and consent to participate

This article does not contain any studies conducted by the authors of this work, and it does not contain any studies involving patients or animals as test subjects. Informed consent was not required for this article.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data availability

Our manuscript has no associated data.

Author contribution

YFM and WA—selected the literature data on the review topic, contributed to the manuscript preparation, and participated in the discussion.

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