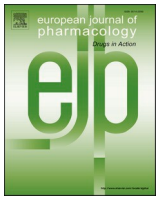
European Journal of Pharmacology 956 (2023) 175958

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar



Antidepressant effects of coumarins and their derivatives: A critical analysis of research advances

Nneka Augustina Akwu [a,b,**], Makhotso Lekhooa [b], Dou Deqiang [c], Adeyemi Oladapo Aremu [a,d,*]

[a] Indigenous Knowledge Systems Centre, Faculty of Natural and Agricultural Sciences, North-West University, Private Bag X2046, Mmabatho, 2790, South Africa
[b] Preclinical Drug Development Platform, Faculty of Health Sciences, North-West University, Private Bag X6001, Potchefstroom, 2520, South Africa
[c] Liaoning University of Traditional Chinese Medicine, 77 Life one Road, DD port, Dalian Economic and Technical Development Zone, Dalian, 116600, China
[d] School of Life Sciences, College of Agriculture, Engineering and Science, University of KwaZulu-Natal, Private Bag X54001, Durban, 4000, South Africa

ARTICLE INFO

Keywords:
Depression
Medicinal plants
Mental health
Monoamine oxidase inhibitors
PRISMA
VOSviewer

ABSTRACT

Coumarins and their derivatives are non-flavonoids polyphenols with diverse pharmacological activities including anti-depressant effects. This study systematically examines the antidepressant effects of coumarins and their derivatives in relation to time series of research progress in the pharmacological pathways, association with other diseases, toxicity and bibliometric analysis. The review was approached using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) coupled with R package involving Biblioshiny, a web interface for Bibliometrix analysis and VOSviewer software analytic tools. Literature searches were conducted in Scopus, Web of Science, and PubMed from the inception through January 21, 2023. Coumarins, depression, coumarin derivatives and treatment were the main search terms used which resulted in the inclusion of 46 eligible publications. Scopoletin, psoralen, 7-hydroxycoumarin, meranzin hydrate, osthole, esculetin/umbelliferone were the most studied coumarins with antidepressant effects. Coumarins and their derivatives exerted antidepressant effects with a stronger affinity for monoamine oxidase-B (MAO-B) inhibition and, their inhibitory effect via neurotransmitter pathway on MAO is well-studied. However, epigenetic modification, neuroendocrine, neurotrophic pathways are understudied. Recent research focuses on their antidepressant effects which targeted cytokines and fibromyalgia. There is a link between the gut microbiome, the brain, and depression; meranzin hydrate exerts an antidepressant activity by remodelling the gastrointestinal system. We established that empirical data on some coumarins and their derivatives to support their antidepressant effects are limited. Likewise, the safe dose range for several coumarins and their derivatives is yet to be fully determined.

1. Introduction

Coumarins are non-flavonoids polyphenols, o-hydroxycinnamic acid lactones (also known as 2H-chromen-2-one1,2-benzopyrone) (Gomez--Pinilla and Nguyen, 2012; Sashidhara et al., 2015), a group of sweet-smelling (aromatic) phytochemicals. Coumarins and their derivatives are structurally distinct (Wu et al., 2009; Sahni et al., 2021) and are being used for the treatment of mental health disorders such as schizophrenia, anxiety, and depression (Irvine et al., 2012; Delogu et al., 2014; Pathak et al., 2016; Abourashed, 2018; Rehuman et al., 2020). Several coumarin derivatives have antidepressant effects e.g., scopoletin, umbelliferone, and 7-hydroxycoumarin (Jo et al., 2002; Qin et al., 2017; Lee et al., 2020b; Nabeel et al., 2021; Heghes et al., 2022; Kılıç, 2022; Sinha et al., 2022).

Currently, an estimated 3560 coumarins have been isolated (Buckingham et al., 1994; Kostova, 2005). However, with the increasing therapeutic usage, more coumarins and their derivatives would have been discovered (Buckingham et al., 1994; Kostova, 2005). There are four major types of natural coumarins *viz.*, simple coumarins, pyranocoumarins, pyrone-substituted coumarins, and furanocoumarins (Murray et al., 1982; Bhattarai et al., 2021). They are widely distributed in different plant parts especially those from the families such as Apiaceae (Umbelliferae), Rutaceae, Asteraceae, Fabaceae and Solanaceae (Estévez-Braun and González, 1997; Khilya et al., 2005; Patil et al.,

* Corresponding author. Indigenous Knowledge Systems Centre, Faculty of Natural and Agricultural Sciences, North-West University, Private Bag X2046, Mmabatho, 2790, South Africa.
** Corresponding author. Indigenous Knowledge Systems Centre, Faculty of Natural and Agricultural Sciences, North-West University, Private Bag X2046, Mmabatho, 2790, South Africa.
E-mail addresses: 49584219@mynwu.ac.za (N.A. Akwu), Oladapo.Aremu@nwu.ac.za (A.O. Aremu).

https://doi.org/10.1016/j.ejphar.2023.175958
Received 20 May 2023; Received in revised form 4 July 2023; Accepted 1 August 2023
Available online 4 August 2023

Table 1
The systematic review search strategy and selection from three databases.

Databases searched	Scopus, Web of Science and PubMed
Search criteria	"Coumarins" OR "coumarin derivatives" AND "depression" OR "depressive disorder" OR "psychological distress" OR "mental health" OR "psychiatric disorder" OR "mood disorder" OR "clinical depression" OR "MDD" OR "anxiety disorder" AND "treatment"
Inclusion criteria	Research papers (full length) on coumarin and its derivatives with a focus on mental disorders using Human or animal models (*in vitro* or *in vitro*).
Exclusion criteria	Articles published in languages other than English Systematic reviews, Meta-analyses, Proceedings, Notes, Reviews, letters, comments, books and book chapters, Research papers on other diseases

2013; Madeiro et al., 2017; Sarker and Nahar, 2017) and in microbes especially bacteria and fungi (Stringlis et al., 2019; Tsivileva et al., 2022).

Millions of people suffer from the mental health illness such as major depressive disorder (MDD) and the global prevalence of mental disorders was about 970 million people, in 2019 (pre-pandemic), of which 28.9% have a depressive disorder (WHO, 2022; Fries et al., 2023). The draw backs such as cost, low efficacy, safety, delayed action, side- and long-term effects associated with the existing antidepressant medications have inclined researchers towards exploring natural products including plants (Pathak et al., 2016; Kenda et al., 2022). The efficacy, safety, and toxicity of plant-based products with medicinal properties should be investigated before usage (Akwu et al., 2019; Bonokwane et al., 2022).

The potential of coumarins and their derivatives in managing mental health have been recognised (Qin et al., 2017; Wang et al., 2019a). The review by Patil et al. (2013) focused on the synthesis of coumarin derivatives as MAO inhibitors for depression and Alzheimer's disease but the study did not use a systematic approach. A systematic approach assessing the relationship between the antidepressant effects of coumarins and their derivatives to aspects such as brain-gut-microbiota, Brain-derived neurotrophic factor [BDNF], drug interaction fields, toxicity and other diseases remain valuable. Additionally, it is pertinent to identify existing gaps in knowledge and the current trend of this effect using bibliometric analysis in a time series-based development. Thus, we qualitatively comprehend and integrate existing studies using a systematized procedure as well as to quantitatively assess the scientific publications on the antidepressant effects of coumarins and their

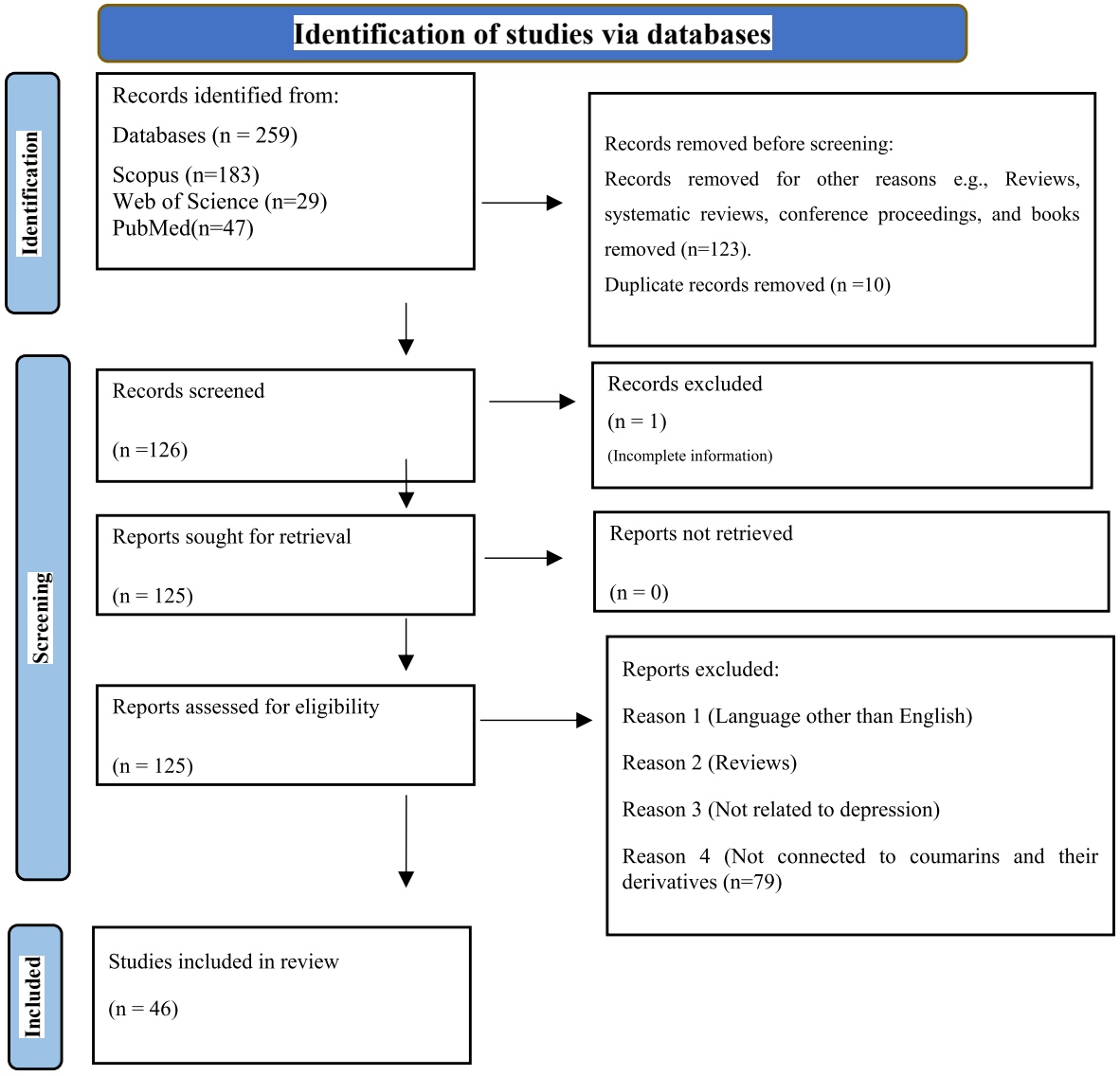
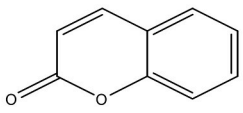
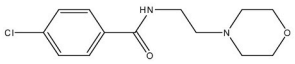


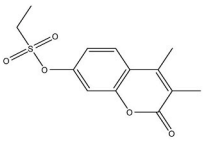
Fig. 1. A methodological flow diagram of the data collection and filtering process using PRISMA protocol.



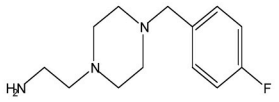
Coumarin



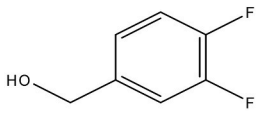
Moclobemide

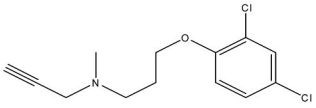


Esuprone



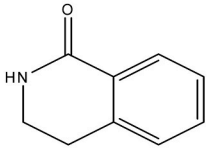
7-(2-(4- (4-fluorobenzyl)piperazin-1-yl)-2-oxoethoxy)-2H-chromen-2-one



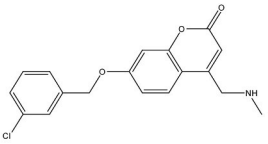


Clorgyline or Clorgiline

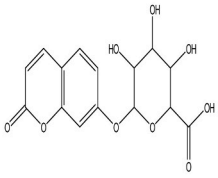
7-[(3,4-difluorobenzyl)oxy]-3,4-dimethylcoumarin



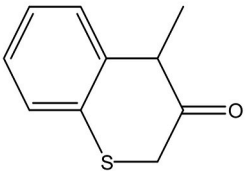
3,4-dihydroisoquinolin-1(2H)-one derivatives



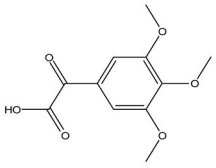
7-(3-chlorobenzyloxy)- 4-(methylamino)methyl-



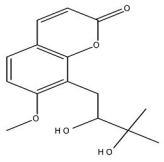
7-hydroxycoumarin (7-HC)



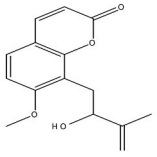
4-thiochromen-3-one class



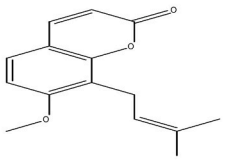
2-oxo-3-(3,4,5-trimethoxyphenyl)propanoic



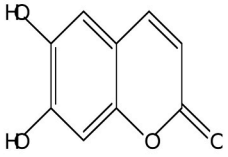
Meranzin hydrate



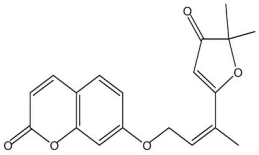
Auraptene



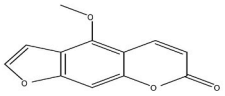
Osthole



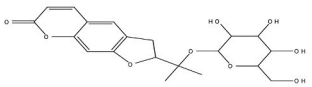
Esculetin



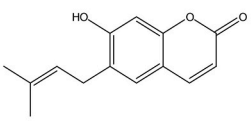
Geiparvarin



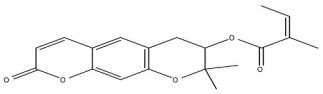
Bergapten



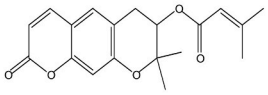
Nodakeni



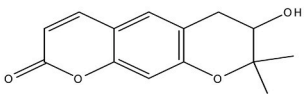
Demethylsuberosin



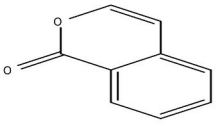
Decursinol



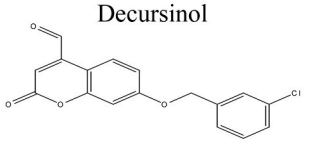
Decursin



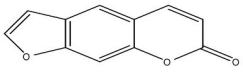
Decursinol



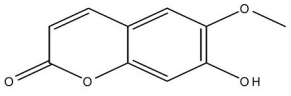
Isocoumarin



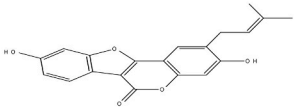
7-(3-chlorobenzyloxy)- 4-



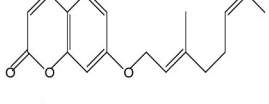
Psoralen



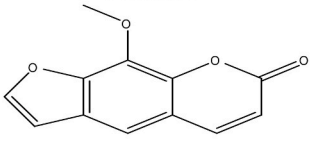
Scopoletin



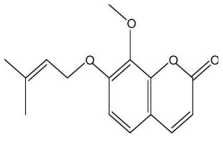
Psoralidin



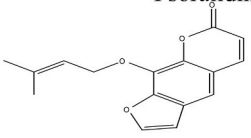
Auraptene



Xanthotoxin



Lacinartin



Imperatorin

Fig. 2. Chemical structures of some coumarins and coumarin derivatives used as antidepressant agents. Source: ChemDraw Pro 8.0.

Table 2
The evaluated dose, plant part, extraction solvent and experimental model of some coumarins and their derivatives.

S/N	Type of coumarin(s)	Evaluated dose and treatment duration	Plant	Plant material	Extraction solvent	Model: *In vitro, in vivo* or *in silico*	Reference
1.	Coumarin analogue Coumarin derivative	5 μL 30 min incubation	*Hibiscus syriacus* (Malvaceae)	Root bark	70% aqueous methanol	Mouse brain (*in vitro*)	Yun et al. (2001)
2.	Scopoletin	1–100 mg/kg, p.o. 2 h (acute stress)	*Polygala sabulosa* A.W. Bennett (Polygalaceae)	Whole plant	96% aqueous ethanol	Female Swiss mice (*in vivo*)	Capra et al. (2010)
3.	Coumarins	N/A	*Areca catechu* L. (Arecaceae)	Nuts	70% methanol	MULTIAQUANT. Compound-disease targets" (*in silico*)	Yang et al. (2021)
4.	Coumarins	10 mL/kg	*Platycodon grandiflorum* (Jacq.) A. DC. (Campanulaceae)	Leaves	70% methanol	Mouse	Wang et al. (2019a)
5.	Coumarins	200 and 400 mg/kg significantly ($P < 0.05$) Acute 7 days (acute) and 14 days of treatments	*Morus alba* (Moraceae)	Leaves	Hydroalcoholic	Mice (*in vivo*)	Askar (2019)
6.	Decursinol, Demethylsuberosin, Decursin, Decursinol angelate and Nodakenin	50 μg/mL	*Angelica gigas* Nakai (Apiaceae)	Root	Methanol	Mouse brain mitochondria (*in vitro)*	Lee et al. (2017)
7.	Furocoumarins	7.5–100 mg/kg 7- or 14-day treatment	*Psoralea corylifolia* L. (Fabaceae)	Seeds	75% aqueous ethanol	Male ICR mice (*in vivo*)	Chen et al. (2005)
8.	7-(6'R-hydroxy-3', 7'-dimethyl-2'E, 7'-octadienyloxy) coumarin, Auraptene, Umbelliferone	50 μL 30 min	*Dictamnus albus* (Rutaceae)	Aerial parts	Methanol	Mouse brain mitochondrial fraction (*in vitro*)	Jeong et al. (2006)
9.	Two furocoumarins (psoralen and isopsoralen)	1–100 μM 10 min	*Psoralea corylifolia* L. (Fabaceae)	Seeds	Methanol, or water and ethanol (1:1 v/v) mixture	Male Sprague-Dawley rat brain mitochondrial fraction (*in vitro*)	Kong et al. (2001)
10.	Psoralen	10, 20, 40 mg/kg 1, 3, 7 days, respectively	*Psoralea corylifolia* L.	Fruit seeds	Methanol	Male ICR strain of mice (*in vivo*)	Xu et al. (2008)
11.	Aesculetin, Aesculetin 7-methyl ether, Scopoletin	100–300 μg/mL	*Artemisia vulgaris* L (Asteraceae)	Whole plant	80% aqueous ethanol	Mouse brain mitochondria (*in vitro*)	Lee et al. (2000)
12.	Lacinartin	250 ug/mL	*Zanthoxylum schinifolium* Sieb. & Zucc (Rutaceae)	Stem	Methanol	Mice (ICR, male) (*in vivo*)	Jo et al. (2002)

derivatives from 1996 to 2023. We applied bibliometric analyses to provide knowledge on the academic productivity, theme trends, knowledge strtucture and forecast trends in subject area. This in-depth review explores the various pharmacological activities of coumarins and their derivatives with a particular focus on their antidepressant effects.

2. Methodological approach

2.1. Data sources: Search strategy for electronic databases, and selection

The literature search ranged from inception to 21 January 2023 in the selected databases (Table 1). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol was used for the literature selection (Page et al., 2021). The articles used for this systematic review were critically assessed *i.e.,* further screened and examined by three experts in the field.

Bibliometric analysis, a method for quantifying and assessing scholarly literature, frequently makes use of bibliographic databases such as Web of Science, and Dimensions (Cobo et al., 2015; Aria and Cuccurullo, 2017). The bibliometrix's graphical user interface (GUI_biblioShiny), was used for the econometric literature analysis (Aria and Cuccurullo, 2017) and VOSviewer (version 1.6.19) was used to assess the co-authorship, bibliographic coupling and co-occurrence (Van Eck and Waltman, 2010). Other software (multidimensional scaling [MDS]) have certain drawbacks especially artefacts (Van Eck et al., 2010).

3. Results and discussion

A total of 259 documents were initially retrieved, while only 46 research publications were eligible after applying the inclusion and exclusion criteria (Fig. 1). The 46 publications (1996–2022) were from 39 sources, with 281 authors of which 2 were single authored, while they were 6.46% co-authors per document. The average citations per document was 20.17. The number of author keywords was 183. The international co-authorship was 23.91%, co-authors per document 6.46 with 2155 references. The average age of the publications was 7.73 with 20.07 average citations per publication. The timespan was 1996–2022 with an annual growth rate of 5.48%.

There are several depression pathways which, include neurotransmitter, inflammatory, neuroendocrine, genetic pathway, cognitive, neurotrophic, environmental, and neuroinflammatory (gut microbiome), and epigenetics modifications (Miller and Raison, 2016; Tafet and Nemeroff, 2016; Jiang et al., 2022; Wei et al., 2022; Liu et al., 2023).

Depression is associated with certain variations in the regulatory pathway of some enzymes e.g., Acetylcholinesterase (AChE), Monoamine oxidase (MAO), and Catechol-O-methyltransferase (COMT) (Mattsson et al., 1972; Belmaker and Agam, 2008). Neurotransmitters such as serotonin, dopamine and norepinephrine play key roles in the lessening symptoms of anxiety and depression. The catalyses of these neurotransmitters by the MAO give rise to an imbalance, hence inhibitors of this enzyme such as tranylcypromine (parnate), isocarboxazid (marplan) and phenelzine (nardil) are important in the treatment or management of depression and anxiety (Fiedorowicz and Swartz, 2004; Pacher and Kecskemeti, 2004). The enzyme, monoamine oxidase (MAO) has two isoforms of MAO namely, MAO-A and MAO-B (Gnerre et al.,

2000; Kong et al., 2001; Carotti et al., 2002). Acetylcholinesterase (AChE) - acetylcholine plays key roles in movement, memory retention and attention (Trzepacz and van der Mast, 2002; Chen et al., 2015; Erdogan Orhan and Ozan Gulcan, 2015). Serotonin, dopamine, and norepinephrine play key roles in modulating symptoms of anxiety and depression. Serotonin [5-HT or 5-hydroxytryptamine] is responsible for social behaviour, controlling appetite, sleep, anxiety, and mood), dopamine controls learning, motivation, movement, attention and happiness while norepinephrine which is the fight or flight response, is responsible for regulating the response to stress, blood pressure, and heart rate. They are all neurotransmitters but for norepinephrine which in addition is a hormone (Udina et al., 2016; Liang et al., 2021; Dhailappan and Samiappan, 2022). The alterations of these neurotransmitters are implicated in depressive symptoms, and also in the mechanism of action of antidepressants classes such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and therapies such as psychodynamic therapy, and cognitive behavioural therapy (CBT) are usually used for the treatment or management of depression, either singly or in combination (Belmaker and Agam, 2008; Marazziti et al., 2012; Hunter et al., 2022; Latimer and Cornett, 2023). Thus, the mechanism of action of most antidepressants is usually via neurotransmitter increment by TCAs, SSRIs and SNRIs or via suppression of their inhibitors.

There are numerous reports on the antidepressant effects of plants [*Hypericum perforatum* (St. John's Wort), *Ginkgo biloba*, *Crocus sativus* (Saffron), grapefruit (*Citrus paradisi*), *Morinda officinalis*, *Curcuma longa* (turmeric)], and their metabolites such as resveratrol, Omega-3 fatty acids, quercetin (in vegetables and fruits), and epigallocatechin gallate (EGCG in green teas) (Liang et al., 2002; Bukhari and Dar, 2013; Cheng et al., 2017; Chen et al., 2019; Hernández-Vázquez et al., 2022). The presence of coumarins and other phytometabolites in some traditional Chinese medicine and endophyte cultures have been implicated as the principle for their antidepressant effects (Tan et al., 2000).

In this review, 31 coumarins and their derivatives were recorded from the eligible literature (Fig. 2), and we focused on their reported antidepressant effects via, neurotransmitter pathway (monoamine alterations), neurotrophic pathway (via BDNF activation), inflammatory pathway (cytokines modulation) and neuroinflammation (brain-gut-microbiome colony restoration). It is noteworthy that these pathways are not mutually exclusive and can relate to one another because depression is caused by synergic combination of factors which include multiple biological alterations of either genes or pathways (Nonen et al., 2016; Udina et al., 2016; Mandal et al., 2022). In addition, the synergy with other diseases in relation to the antidepressant effects of coumarins and their derivatives remain prominent.

3.1. Pharmacological pathways of the antidepressant effects of coumarins and their derivatives

The different pharmacological activities of coumarins and their derivatives is linked to their ability to suppress myosin light chain kinase; restrict the development of the mitotic spindle, which results in cell death, and reduce tyrosine phosphorylation (Wu et al., 2009), while their antidepressant effects may be attributed to their antioxidant and anti-inflammatory properties (Matés et al., 1999; Sulakhiya et al., 2016; Dhiman et al., 2018; Singh et al., 2020; Hasan et al., 2021; Sharma et al., 2022).

Several investigations on the antidepressant effects of coumarins and their derivatives using different dose, various plant parts, extraction solvents and biological systems (*in vitro, in vivo,* and *in silico* models) have been conducted (Table 2). The antidepressant effects of some coumarins and their derivatives have been investigated in animal models. For example, coumarin regulates the level of dopamine; 7-hydroxycoumarin (7-HC) increases the brain's levels of norepinephrine and serotonin; 4-thiochromen-3-one class coumarin derivatives inhibits monoamine transporters, 2-oxo-3-(3,4,5-trimethoxyphenyl) propanoic acid (TMPA) inhibits norepinephrine transporter (NET) and serotonin transporter (SERT). Scopoletin present in *Scopolia japonica, Polygala sabulosa*, *Hibiscus syriacus* and umbelliferone, a coumarin derivative also exhibits antidepressant activity (Yun et al., 2001; Capra et al., 2010; Monadi et al., 2021). The ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) of the methanol-water extracts of *Areca catechu* L. (Betel nuts - kernel and

Table 3
The inhibitory values (IC_{50}/$_pIC_{50}$) of some coumarins and their derivatives against monoamine oxidases.

Monoamine oxidase (MAO) isoforms	Compounds	IC_{50}/ $_pIC_{50}$	Reference
MAO	Auraptene	1.70 μM	Jeong et al. (2006)
	7-(6'R-hydroxy-3', 7'-dimethyl-2'E, 7'-octadienyloxy) coumarin	0.70 μM	Carotti et al. (2002)
	Xanthotoxin	64.60 μM	Carotti et al. (2002)
	Umbelliferone	87.50 μM	Jeong et al. (2006)
	Lacinartin	9.20 μM	Jo et al. (2002)
	Scopoletin	19.40 μg/mL	Yun et al. (2001)
	Scopoletin	45.00 μmol	Lee et al. (2000)
	Aesculetin a.k.a cichorigenin, 6,7-dihydroxycoumarin and esculetin	30.10 μmoL	Lee et al. (2000)
	Aesculetin 7-methyl ether	32.20 μmoL	Lee et al. (2000)
MAO-A	Auraptene	34.60 μM	Jeong et al. (2006)
	7-(6'R-hydroxy-3', 7'-dimethyl-2'E, 7'-octadienyloxy) coumarin	1.30 μM	Carotti et al. (2002)
	Desmethyl congener	4.62%[a]	Carotti et al. (2002)
	Geiparvarin	4.57%[a]	Carotti et al. (2002)
	3,4-dimethylgeiparvarin	37% (10 M)[a]	Carotti et al. (2002)
	3,4-dihydro-2(1H)-quinolinone derivatives	6.89%[a]	Carotti et al. (2002)
	Psoralen	15.20 μM	Kong et al. (2001)
	Isopsoralen	9.00 μM	Kong et al. (2001)
	Lacinartin	5.70 μM	Jo et al. (2002)
	7-[(3,4-difluorobenzyl)oxy]-3,4-dimethylcoumarin	1.14 nM	Gnerre et al. (2000)
	Decursin	1.89 μM	Lee et al. (2017)
MAO-B	Auraptene	0.60 μM	Jeong et al. (2006)
	Lacinartin	28.60 μM	Jo et al. (2002)
	7-(6'R-hydroxy-3', 7'-dimethyl-2'E, 7'-octadienyloxy) coumarin	0.50 μM	Carotti et al. (2002)
	Desmethyl congener	7.55%[a]	Carotti et al. (2002)
	Geiparvarin	6.84%[a]	Carotti et al. (2002)
	Psoralen	61.80 μM	Kong et al. (2001)
	Isopsoralen	12.80 μM	Kong et al. (2001)
	Decursinol angelate	–	Lee et al. (2017)

[a] pIC50 (the potency or inhibitory activity of a compound in pharmacology and drug discovery.

peel), which is a Chinese traditional medicine, revealed the presence of coumarins in the extract among the diverse phytochemicals (Yang et al., 2021). Likewise, the dried leaves of *Platycodon grandiflorum* (Jacq.) A. DC., (Wang et al., 2019a) and the hydroalcoholic leaf extract of *Morus alba* contain coumarins and exerted antidepressant effects (Askar, 2019). Certain coumarins and their derivatives have a significant blood-brain barrier (BBB) permeability and selectivity, which is indicative of a good pharmacokinetic potential hence they are promising for drug development (Herbet et al., 2022).

3.1.1. Inhibition of monoamine oxidase (MAO) by coumarins and their derivatives

Monoamine oxidase (MAO) breakdown neurotransmitters such as dopamine, norepinephrine, and serotonin by inhibiting MAO, the availability of the neurotransmitters in the brain increases and subsequently depression-like symptoms were alleviated. Several coumarins and their derivatives associated with MAO inhibition (MAOI) exhibit antioxidant effects particularly coumarins with a methoxy group at position 7 (Gnerre et al., 2000; Sairam et al., 2007; Dhiman et al., 2018). There are two isoforms of MAOIs and they are classified based on their substrate *viz*., MAO-A and MAO-B (Gnerre et al., 2000; Sairam et al., 2007). For instance, MAO-A such as minaprine, toloxatone and brofaromine exert influence on dopamine, melatonin, epinephrine, serotonin, melatonin, and norepinephrine. On the other hand, MAO-B including lazabemide, and rasagiline exert influence on trace amines, phenylethylamine, dopamine. There are the amphi-MAOIs i.e., non-selective MAO-A/B inhibitors such as furazolidone, pheniprazine, and benmoxin (Gnerre et al., 2000). MAO-B reacts on benzylamine and phenylethylamine while MAO-A has a stronger affinity for norepinephrine and serotonin (Sairam et al., 2007).

The inhibition of MAO enzyme may be irreversible or reversible. The reversible inhibitors have weak bonds with the MAO enzyme and can be eventually displaced from it, allowing the enzyme to regain its activity, while the irreversible inhibitors adhere to the enzyme tightly and irreversibly inactivate it (Ramsay, 2012; Kaczmarczyk et al., 2020). The reversible MAOIs can be eliminated from the body quickly, are less likely to cause long-term adverse effects, and are generally considered safer than irreversible MAOIs (Ramsay, 2012; Kaczmarczyk et al., 2020). Decursin is an example of reversible MAOIs, while isocoumarin and 7-hydroxycoumarin and clorgyline are examples of the irreversible MAOIs. Lee et al. (2017) isolated five coumarins (decursinol, demethylsuberosin, decursin, decursinol angelate and nodakenin) from the roots of *Angelica gigas* Nakai and tested them against human MAO inhibitory properties for the treatment of conditions such as depression, Parkinson's, and Alzheimer's disease. Neither MAO-A nor MAO-B enzymes were effectively inhibited by nodakenin, demethylsuberosin, and decursinol. MAO inhibition was exhibited by the structurally related compounds, decursin and decursinol angelate (Table 3). Decursin was highly effective than decursinol angelate. In addition, the IC_{50} value was comparable to that of toloxatone, a commercial antidepressant drug.

Based on the study by Dhiman et al. (2018), the impact of the hybrid coumarin and 5-bromo-2-oxoindolin-3-yl ring with hydrazine binder on the (human) hMAO-A active site revealed a significant hMAO-A inhibitory capacity of one of the tested compounds known as 5-bromo-isatin (7.473 μM). They further conducted computational studies and observed that a strong relationship between the docking score and experimental MAO inhibition. Geiparvarin, a coumarin isolated from *Geijera parviflora* Lindl inhibited MAO (Dreyer and Lee, 1972; Jerris and Smith, 1981). Geiparvarin and its analogues were observed to efficiently inhibit the two monoamine oxidase isoforms (MAO-B and MAO-A) differently. Desmethyl congener, one of the tested compounds, was found to be a potent and specific MAO-B inhibitor, greater than its parent compound geiparvarin (Table 3). In addition, using molecular modelling and X-ray crystallography, the observed activity variations was linked to the removal of some steric hindrance from its methyl group in position 3 (Carotti et al., 2002).

The simple coumarin, and derivatives of 3,4-dihydroisoquinolin-1(2*H*)-one are structurally related, having nitrogen or carbon atoms in the ring and a six-membered ring with a double bond in common (Fig. 1). According to Bester et al. (2022), 3,4-dihydroisoquinolin-1(2*H*)-one antidepressant effect may be linked to it its structural relatedness with coumarin. This may imply that compounds that are structurally related to coumarin may also induce antidepressant effects. Gnerre et al. (2000) tested the effective inhibition of 71 coumarins derivatives against MAO-A and MAO-B. They found that 3,4-dihydro-2(1H)-quinolinone derivatives significantly inhibited MAO-B (Table 3). Based on the findings by Gnerre et al. (2000), out of the 71 coumarin derivatives investigated, a number of the coumarins investigated demonstrated more convincing interactions with MAO-B. The compound 7-[(3,4-difluorobenzyl)oxy]-3,4-dimethylcoumarin, exhibited the most effective MAO-B inhibition (Table 3).

Chen et al. (2005) observed that furocoumarins present in the seeds of *Poralea corylifolia* exhibited preference for MAO-B inhibition. Jeong et al. (2006) observed that auraptene and 7-(6'R-hydroxy-3', 7'-dimethyl-2'E, 7'-octadienyloxy) coumarin exhibited preferential inhibition against MAO-B. The coumarin compounds synthesised by Mangiatordi et al. (2017) were specific to MAO-B. The methanol extracts of *Dictamnus albus* aerial parts contains the following coumarins; (6'R-hydroxy-3', 7'-dimethyl-2'E, 7'-octadienyloxy) coumarin, xanthotoxin, umbelliferone and auraptene. All the coumarins inhibited MAO at varying concentrations as quantified by the IC_{50} values (Table 3), and with affinity to MAO-B (Jeong et al., 2006).

This pattern of preference to MAO-B inhibitors has been reported in several neurodegenerative diseases including Alzheimer (Matos et al., 2020; Rodriguez-Enriquez et al., 2020; Carneiro et al., 2021). On the contrary, Kong et al. (2001) observed that two furocoumarins (psoralen and isopsoralen) obtained from *Psoralea corylifolia* L., specifically inhibited MAO-A over MAO-B. Psoralen has been isolated from *Cullen corylifolium* (L.) Medik and *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. (Kong et al., 2001; Chen et al., 2005; Xu et al., 2008). Based on the study by Lee et al. (2000), the authors revealed a significant MAO inhibitory properties of three coumarins, aesculetin, esculetin-6-methylether, and scopoletin, isolated from the perennial weed *Artemisia vulgIaris* (mugwort). Isocoumarin, decursin and clorgyline were selective towards MAO-A (Lee et al., 2017; Koyiparambath et al., 2021; Guglielmi et al., 2022). Coumarins are considered as key MAOs inhibitors because of their simplicity in synthesis, great therapeutic potential, and reversible ability to block MAOs (Koyiparambath et al., 2021).

Drug-drug interaction has been of concern to many researchers especially for those in the pharmaceuticals because of resistant to treatment and side effects such as psychotic relapse, extrapyramidal effects (Guieu et al., 2021; Shrivastava et al., 2022). The potential drug interaction (PDI) of coumarins and other medications observed among cancer patients receiving IV therapy who are ambulatory lead to the recommendation that the screening of these drugs (PDI) should be done before chemotherapy (Van Leeuwen et al., 2011).

For some coumarins, the drug interaction is attributed to modulatory inhibitory lipophilic interactions than electronic/electrostatic interactions (Gnerre et al., 2000). Implying that lipophilic and electrostatic are the only MAO activity modulators. However, another report indicated that lipophilic, electrostatic, and steric are the modulate effects of MAO-A and B (Catto et al., 2006). This differential modulatory observation is believed to be a consequence of structural differences in coumarins (Vilar et al., 2012). The selectivity of MAO-A and B inhibitors, lipophilic and steric fields were not as significant as electrostatic fields in determining the selectivity of the enzyme (Catto et al., 2006).

Hampel et al. (1996) investigated the drug-drug interaction of amitriptyline (an antidepressant) and a coumarin derivative, phenprocoumon an anticoagulant and the authors observed thrombinemic effects. However, due to the small sample size (7), the authors

acknowledged that their experimental observation cannot be conclusive. Monastero et al. (2007) observed a drug-drug interaction between a synthetic coumarin anticoagulant acenocoumarol (warfarin) and duloxetine in humans. A drug-drug interaction precisely antagonism was reported by Schurr and Livne (1976). The authors reported that cannabidiol (CBD) counteracts the effect of Δ^1-THC on MAO brain mitochondria.

Side effects such as headaches and high blood pressure are due to off-target inhibition, which happens when certain drugs react with flavoenzymes other than MAO (Ramsay et al., 2016; Bester et al., 2022). The type and location of the major drug-enzyme interactions have a significant impact on the potency and selectivity of MAO inhibitors. Drug design can be done by selectively blocking either the MAO-A or MAO-B enzymes, or both. This blocking may result in different degrees of potency by targeting specific regions of the active site and utilising non-covalent interactions. Two '2H-chromene-2-one' compounds (compounds 1 and 2) both linked to active coumarin moiety, which served as molecular probes were used to understand the molecular basis of human MAOs (hMAOs) selectivity. They inhibited hMAO-A and hMAO-B with good isoform specificity (hMAO-B) (Mangiatordi et al., 2017). Sertraline a synthesised salt was linked to a moiety coumarin-3-carboxylate anion (SerH-CCA), and exerted antidepressant activity (Escudero et al., 2016). An investigation of three coumarins (bergapten, umbelliferone and xanthotoxin) revealed prolonged behavioural effects of nicotine in animal models of depression, as well as memory, and learning (Budzynska et al., 2016). The authors concluded that nicotine's procognitive and antidepressants effects were extended. As antidepressant and memory-enhancing effects are one of the primary causes of nicotine dependence, these coumarins may present a novel approach to the treatment of nicotinism. However, nicotine and coumarins administered independently had no effect on the locomotor activity of mice 60 min after dosing (Budzynska et al., 2016).

In a mouse brain, a 250 μg/mL methanol extract of *Zanthoxylum schinifolium* Siebold & Zucc. stem exhibited strong inhibitory effect against MAO (Jo et al., 2002). The hydro-ethanol extract of *Synedrella nodiflora* (L.) Gaertn, had antidepressant property mediated by enhanced noradrenergic and serotoninergic processes (Amoateng et al., 2018). The preliminary qualitative phytochemical screening and high-performance liquid chromatography (HPLC) of the extract revealed the presence of coumarins. The brain and liver of pigs have been used to evaluate MAO inhibitory effects (Schurr and Livne, 1976). Hashish extracts, a drug from *Cannabis* sp. was tested on porcine brain and liver mitochondria and the effect was more significant when compared to the other tested compound [Δ^1-tetrahydrocannabinol (Δ^1-THC)] (Schurr and Livne, 1976). They further concluded that the mechanism of cannabinoid potency was tissue specific as it had no effect on the liver mitochondria MAO at 19 μg/mg. This observation may have been influenced by the tested concentration, and not time because the effect of further exposure duration was investigated.

Two coumarin derivatives (scopoletin and umbelliferone) isolated from the methanol extract of *Biebersteinia multifida* DC roots had the potential to treat anxiety disorders including depression (Monsef-Esfahani et al., 2013). The authors observed a significantly better response relative to the standard drug diazepam (a commonly used anxiolytic drug). Thus, the root extract of *B. multifida* may be an effective natural treatment for anxiety disorders.

3.1.2. Brain-gut-microbiota and the antidepressant effects of coumarins and their derivatives

Recently, neuroscience studies on depression using animal and translational models have been drawn to the brain-gut-microbiota axis theory. This postulates a link between the gut microbiome and the brain, which is bidirectional communication between the gut bacteria and the brain as well as between the microbes and the brain (Moloney et al., 2014; Dinan and Cryan, 2017; Winter et al., 2018; Tremblay et al., 2021). Changing the gut microbiota may be a viable treatment for mental disorders including depression (Moloney et al., 2014; Chong et al., 2019). To fully comprehend the mechanisms underpinning the brain-gut axis and the function it plays in depression, more research especially from clinical trials is necessary.

In China, meranzin hydrate (an organic coumarin derivative) is a commonly prescribed antidepressant, and it has been isolated from *Citrus aurantium* L. (Nie et al., 2022). *Phebalium tuberculosum*, *Murayа paniculata* and *Triphasia trifolia* have anti-depressive properties through alpha 2-adrenoceptors (Xie et al., 2013; Liu et al., 2021). In addition, Xie et al. (2013) linked this antidepressant property to the ability of meranzin hydrate to rebuild the gastrointestinal through the alpha 2-adrenoceptor and ghrelin levels. Hence, its involvement in the brain-gut-microbiota cannot be over-emphasised. Other coumarins and their derivatives may be inducted in the improvement of the gastrointestinal function but are yet to be explicitly evaluated. Hence, it is imperative that more research in this regard should be given utmost attention. To buttress on this, Martelli et al. (2009) and Lee and Park (2000) independently noted that the use of certain antidepressant negatively affected the gastrointestinal movement and thus resulted in depression.

3.1.3. Inflammatory pathway: antidepressant effects of coumarins and their derivatives on chronic inflammation

Neuroinflammation occurs via the modulation of the either mitogen-activated protein kinase (MAPK) pathways or nuclear factor kappa B (NF-κB), and these pathways are associated with the development of depression. The occurrence of these inflammation signalling pathways activates pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumour necrosis factor-alpha (TNF-α) in different cell types (Roohi et al., 2021; Troubat et al., 2021). These pro-inflammatory cytokines can harm neurons and impair their function. The inflammation of the brain and oxidative stress may contribute to the development of depression (Dikmen et al., 2004; Troubat et al., 2021; Behl et al., 2022; Porter and O'Connor, 2022). Hence, an increase in the body's antioxidants will avert oxidative stress and inflammation because antioxidants can aid in defending cells against harm from reactive oxygen species and free radicals. A comprehension of the complexity and full understanding of the link among neuroinflammation, antioxidants, and depression will contribute to alternative and adjunctive treatment of depression.

According to the network pharmacology, *Areca catechu* L. which contains dihydro-p-coumaric acid (phloretic acid) and other metabolites may have an impact on signalling pathways connected to inflammation and as a result, may be useful in the treatment of depression (Yang et al., 2021). The MAPK pathway has been demonstrated to be inhibited by umbelliferone (Wang et al., 2019b; Hassanein et al., 2020) and osthole (Zhou et al., 2019; Singh et al., 2021), which also results in lower synthesis of cytokines that promote inflammation. Hence, these two coumarins may be exerting their antidepressant activity via the inflammatory pathway.

3.1.4. Brain-derived neurotrophic factor (BDNF) and the antidepressant effects of coumarins and their derivatives

The BDNF is a protein that plays a key role in the growth, development, and maintenance of nerve cells (neurons) found in the brain and peripheral nervous system. The action occurs in forebrain regions, especially the hippocampus, making BDNF an important factor in the effectiveness of antidepressants because of its link with depression and other mood disorders (Wang et al., 2008; Björkholm and Monteggia, 2016; Zhang et al., 2022). Serotonergic and dopaminergic neurotransmission is significantly influenced by BDNF through its control of neuronal development (Studer et al., 1995). Treatment with imperatorin and scopoletin dramatically elevates the protective factor BDNF in the brain of rats (Wang et al., 2013) and under *in vitro* condition using astrocytes of rats (Patel et al., 2016), respectively.

Esculetin decreased the depressive-like behaviours in mice while

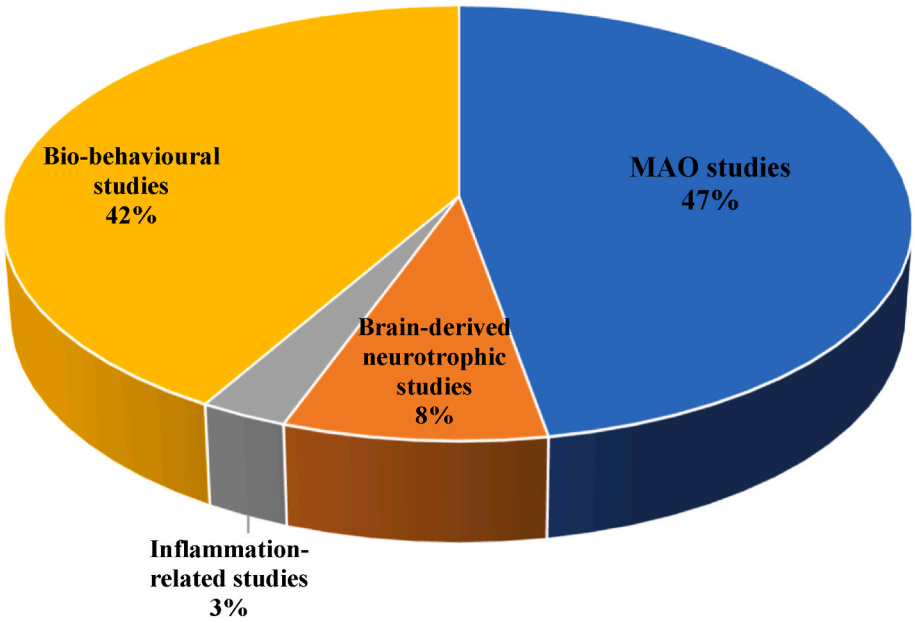


Fig. 3. Studies percentage frequency on the different pathways of antidepressant effects of coumarins and their derivatives (n=36).

raising levels of brain-derived neurotrophic factor (BDNF), and as esculetin decreased the levels of pro-inflammatory cytokines in the brain, it is indicative that its antidepressant pathway is through its ability to reduce inflammation (Zhu et al., 2016). This is an indication that the pathways are not mutually exclusive of one another.

A limited number of research has been conducted on the brain derived neurotrophic (8%) and inflammatory (3%) pathways of the antidepressant effects of coumarins and their derivatives (Fig. 3). Therefore, this area provides opportunities for researchers to explore in attempt to gain better understanding.

3.1.5. Bio-behavioural studies on the antidepressant effects of coumarins and their derivatives

The risk of depression may increase by certain environmental factors such as abuse, and trauma. The first animal model report on the antidepressant effects of drugs was by Porsolt et al. (1977b), which was the forced swimming test (FST). The tail suspension test (TST) was later introduced by Steru et al. (1985). In animal models especially with the use of rodents, two types of tests namely FST and TST, are frequently used to investigate the antidepressant properties of chemicals/drugs (Porsolt et al., 1977a; Chen et al., 2005; Xie et al., 2013; Wu et al., 2015; Park et al., 2018; Askar, 2019; Kaur et al., 2019; Wang et al., 2019a; Hernández-Vázquez et al., 2022). In addition to FST and TST, other type of behavioural test are sucrose preference test (SPT) (Wang et al., 2019a), elevated plus maze (EPM), open field test (OFT) (Monsef-Esfahani et al., 2013; Sulakhiya et al., 2016; Park et al., 2018).

Based on the study by Wang et al. (2021), the most potent antidepressant among the tested compounds was 7-(2-(4-(4-fluorobenzyl) piperazin-1-yl)-2-oxoethoxy)-2H-chromen-2-one. In the FST and TST test models, the compound increased the level of 5-HT in the mouse brains. Hence, the authors concluded that it may operate as a mediator for the antidepressant action of coumarin derivatives. The outcomes of molecular docking showed that the compound interacted significantly with the amino acids close to the active site of the homology model 5-HT1A receptor. The traditional Korean remedy *Gyejibokryeong-hwan* (GBH) and its possible antidepressant benefits on mice with reserpine-induced depression was investigated and of the eight marker compounds found in GBH that were confirmed via HPLC analysis was coumarin (Park et al., 2018). The findings suggested that patients who suffer from depression may benefit from GBH treatment.

Two coumarins (auraptene and meranzin) present in immature fruits of *Citrus aurantium* L. were identified by Chen et al. (2012). After treatment with the aqueous extract of *C. aurantium* L., Wu et al. (2015) found that the mice utilized for the FST and TST had a significantly shorter immobility time. The aqueous, hexane, methanol, and dichloromethane extracts of the aerial parts of *Tagetes lucida* Cav. were tested on rats using FST, and only the aqueous extract exhibited antidepressant effects via serotonergic system (Gabriela et al., 2012). The antidepressant activity of auraptenol present in *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. was considerably reduced by the specific 5-HT1A receptor antagonist WAY100635 (Gu et al., 2014). The current investigation showed that auraptenol significantly decreased the immobility time following acute administration in the TST and FST in mice at systemic dosages of 0.2 and 0.4 mg/kg. Auraptenol had an insignificant impact on locomotor activity in the third behavioural test due to the selective serotonin 5-HT_{1A} receptor antagonist WAY100635. *Ferula assafoetida* L. (Asafoetida) used to treat depression (Alqasoumi et al., 2011; Alqasoumi, 2012), the extract contained coumarin derivatives and other phytometabolites (Alqasoumi, 2012). The antidepressant effect of meranzin hydrate was tested using the FST model of depression (Xie et al., 2013). The dry root of *Angelica dahurica* is listed in the Chinese Pharmacopoeia. It is a rich source of coumarins and furanocoumarins, among them coumarin, scopoletin, psoralen, xanthotoxin, bergapten, isoimperatorin imperatorin byakangelicol, oxypeucedanin and phellopterin, which were present in the methanol extracts of the dried roots of *Angelica dahurica*. Nie et al. (2022) investigated the antidepressant effect of meranzin hydrate by assessing its effects on a rat model of depression and they developed a competitive endogenous RNA (ceRNA) network responsive to the meranzin hydrate therapy. They further gave insights into the molecular mechanisms involved in treating mental health issues, including the Wnt signalling pathway, the axon guidance pathway, and the MAPK signalling pathway, which are all connected to depressive-like behaviour treatment according to KEGG pathways.

3.2. Implications of the antidepressant effect of coumarins and their derivatives with other diseases

Depression has been linked with other diseases such as Alzheimer's disease (Korczyn and Halperin, 2009), diabetes mellitus (Sarwar et al., 2022) and schizophrenia (Apweiler et al., 2022). Kallitsakis et al. (2017) utilized coumarin derivatives to create 1,3-dipolar cycloaddition

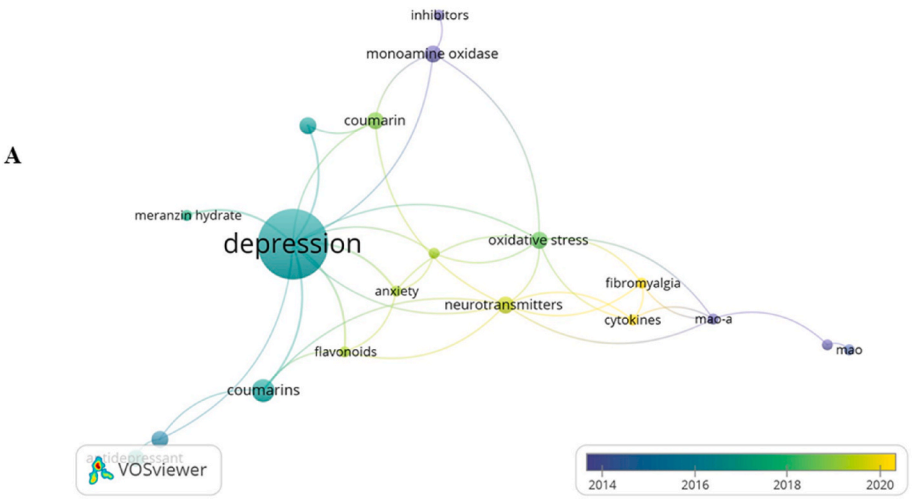


Fig. 4. (A) Graphical (overlay visualisation) representation of author keywords co-occurrence and (B) Word cloud on the antidepressant effects of coumarins and their derivatives. The keywords' frequency of occurrence is specified by the size of the nodes. The co-occurrence of the nodes (keywords) in the same publication is shown by the curves connecting them. The more often two keywords appear together, the closer the distance between them. Word cloud based on authors' keywords generated by Biblioshiny: The analytics automatically registered 50 keywords that appeared more than 8 times. The text size indicates how frequently the words appeared.

reactions with nitrile oxides, for the treatment of Alzheimer's disease, these coumarin-based compounds also functioned as AChE and MAO inhibitors. The novel chemicals created from these coumarins exhibited antioxidant activity and inhibited MAO-B and AChE. This agrees with the report of Sloley et al. (2000), which indicated that MAO-B inhibitors have antioxidant activity.

An amino acid compound (AAC) derivative termed (AAC2), was synthesised from the AAC peptides produced by Lee et al. (2020a) *via* the addition of 7-(diethylamino) coumarin-3-carboxamide side-chain moiety. The authors discovered that it improved glucose regulation in humans and decreased anxiety-related behaviour in mice. An *in vitro* assay on PI3K and AMPK signalling using coumarins was observed to reduce blood glucose and improve insulin sensitivity by improving glucose uptake through activation of the PI3K and AMPK (Jang et al., 2020). Two novel coumarin-based compounds, KIT\C and KIT H were effective on the GPR55 receptor, which has less adverse effects than other medications used to treat neurological diseases such as depression, and schizophrenia. They have been found to alleviate symptoms associated with these diseases (Apweiler et al., 2022).

In terms of occurrence and progression, pain and depression often coexist (Nekovarova et al., 2014). Treatment with osthole improved cognitive deficits, reduced anxiety and depression-like behaviours in rats that had undergone ovariectomy (Adu-Nti et al., 2021). In a study conducted using reserpine-induced pain-depression dyad in mice; two coumarins; skimmetin (umbelliferone) and osthole were administered (Singh et al., 2021). Findings from the study revealed that skimmetin/osthole therapy may prevent neurotransmitter dysregulation caused by inflammation and oxidative stress, thus having an effect on depression. Reserpine mitigation in fibromyagia (a pain syndrome) treatment elevated depression and caused reduced motor coordination in mice. However, the depressive traits reduced when imperatorin a natural furanocoumarin at 10 mg/kg was administered to mice (Kaur et al., 2019). Esculetin, a powerful antioxidant produced from coumarin, decreased anxiety and depressive-like behaviour. Therefore, esculetin can be used to treat psychiatric conditions linked to inflammation and oxidative stress (Sulakhiya et al., 2016). Nodakenin, a coumarin derivative reduces depression-associated memory impairment in mice *via* anticholinergic scopolamine (Jameel et al., 2016).

3.3. Toxicity of coumarins

Even though coumarins and their derivatives have several advantages, the Federal Drug Administration (FDA) of USA classify them as toxic, and as a result, their use as food additive is prohibited (Egan et al., 1990; Byrden, 1995; Bovell-Benjamin and Roberts, 2016). The independent studies of Byrden (1995), Born et al. (2003), and Ratanasavanh et al. (1996) concur that coumarins are toxic. However, Byrden (1995) emphasized that toxicity observed in experimental rat models cannot be

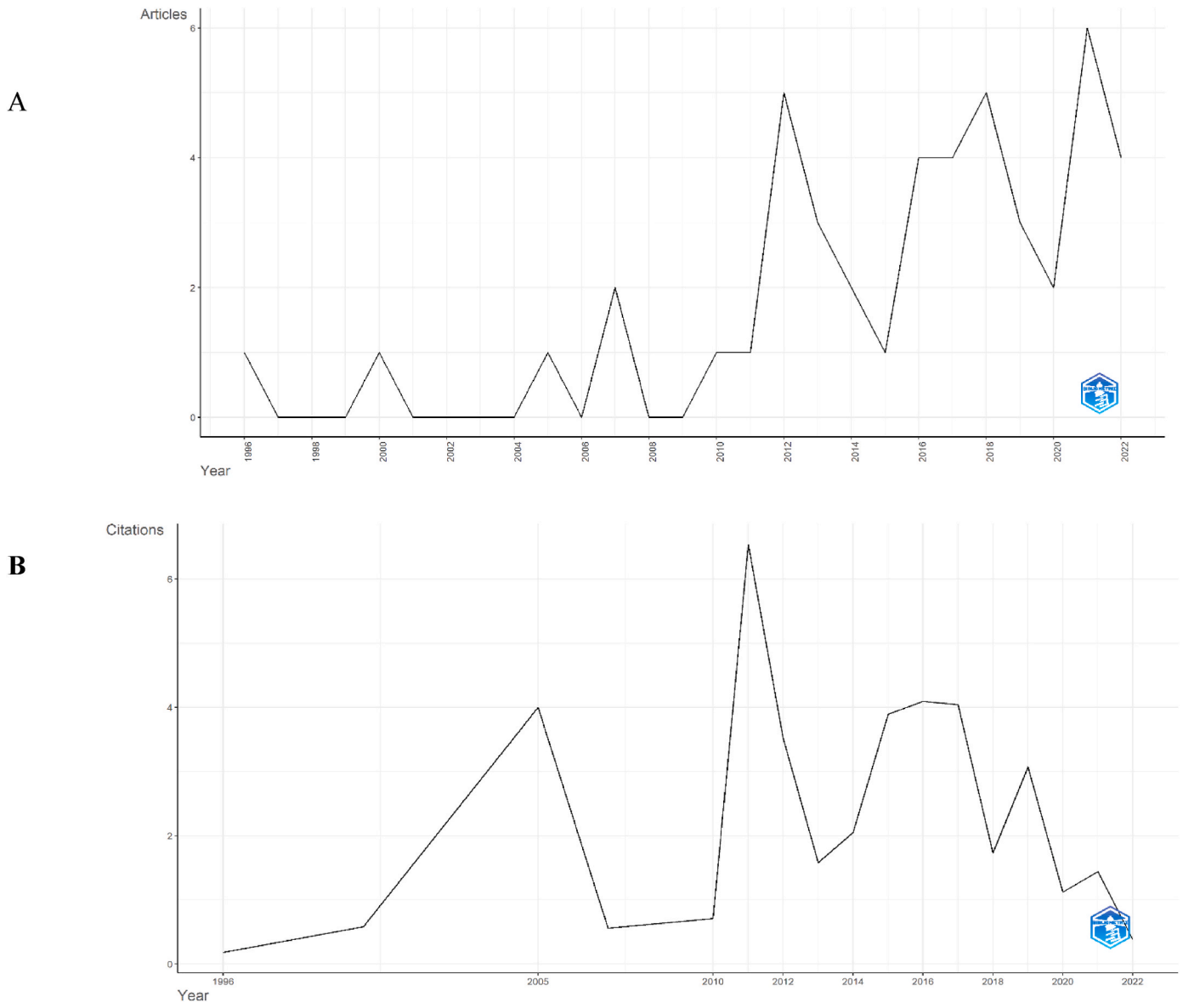


Fig. 5. (A) Annual scientific research publications associated with the antidepressant effects of coumarins and their derivatives from 1996 to 2022. (B) Average research publications citations associated with the antidepressant effects of coumarins and their derivatives per year; from 1996 to 2022.

accurately extrapolated to human toxicity due to differences in human and rat metabolism. It is likely that the toxicity is dose-dependent rather than inherent to coumarins. The use of coumarins and their derivatives at moderate or effective concentrations may be a long-term solution, provided the benefits outweigh the drawbacks. Additionally, long-term consumption may be detrimental to human health (Bovell-Benjamin and Roberts, 2016). The European Union has set a maximum coumarin content in food items at 10 mg/kg (Duns, 2013).

3.4. Bibliometric analysis: The who, what, how, and where in relation to studies on the antidepressant effects of coumarins and their derivatives

3.4.1. Keywords: main themes of publications

The bibliometric analysis of author keywords co-occurrence network (KCN) that were submitted from the 46 publications' authors keywords with at least two times co-occurrence was conducted. In total, 21 of the 183 keywords (authors keywords) passed the threshold for further analysis. There were six clusters with a total link strength of 42. The significant keywords in each cluster are as follows: purple: "depression" "meranzin hydrate"; blue: "coumarins", "mice", "antidepressant"; yellow: "anxiety" "flavonoids" and "neuroinflammation"; green: "coumarin", "monoamine oxidase" "inhibitors"; red: "neurotransmitters", "oxidative stress", "MAO-A"; turquoise: "pharmacophore" and "MAO". These are among the top keywords that at appeared more than any other in each cluster (Fig. 4A). In 2014, the research focus was on MAO and their inhibitors, but "cytokines" and "fibromyalgia" are gaining grounds in recent depression related research trend (Fig. 4A). Fibromyalgia may be a new research trend because of the commonality with depression in terms of pathophysiology and thus both diseases are mostly treated with the same drugs having dual actions on serotonergic and noradrenergic systems. To display the frequency of author keywords, a word cloud was constructed. The statistics showed that "depression" was the most frequently used keyword, followed by "coumarins", "antidepressant" (Fig. 4B). The less frequently used words were "allosteric inhibitors", "Alzheimer's disease", "chalcones", "betel nut" and "antifungal". A significant diversity of keyword trends is an indication that a mosaic pyramid paradigm of research fields can emerge.

3.4.2. Publication trend from 1996 to 2022

The most prominent authors, publications, countries, and journals

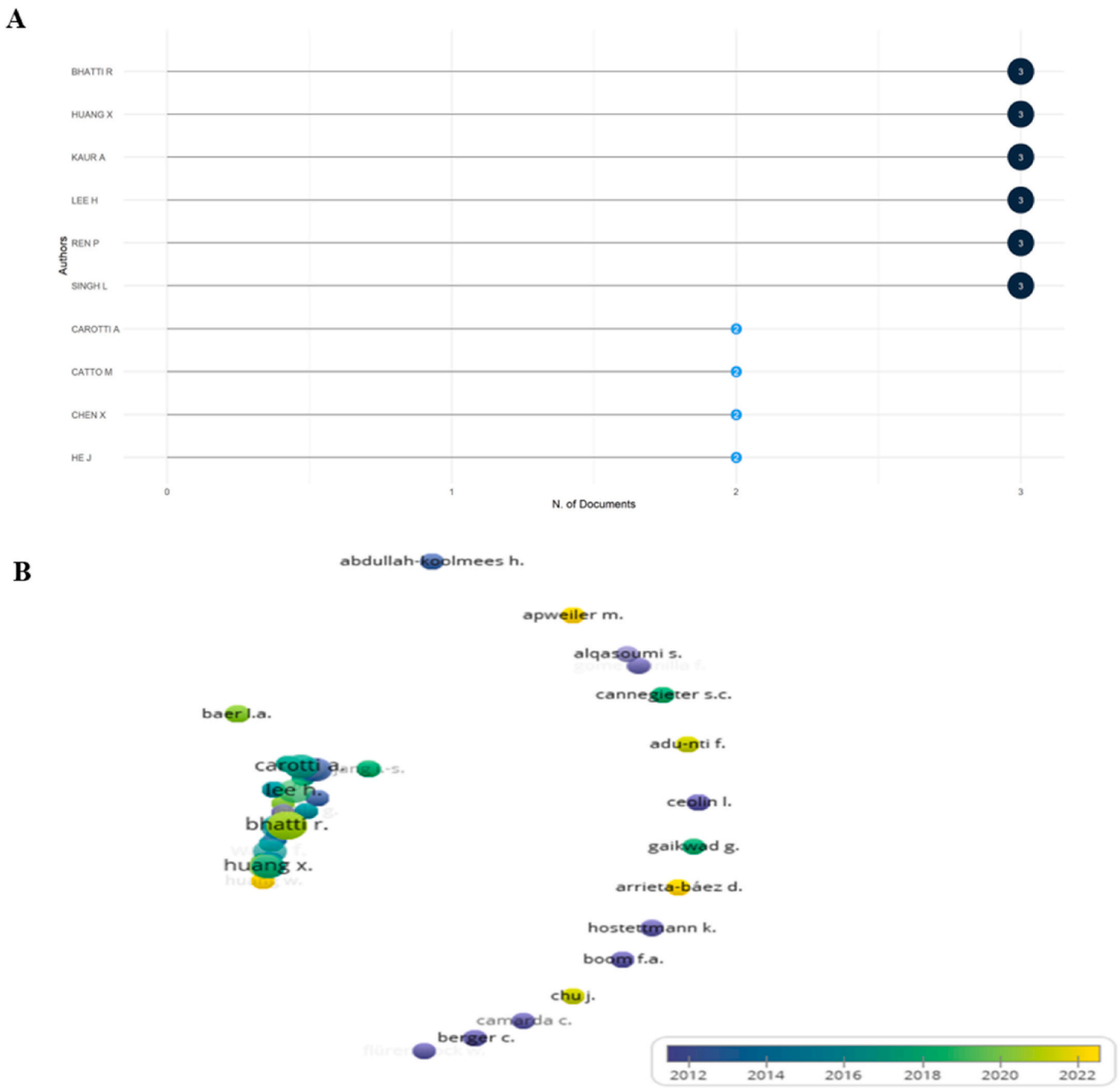


Fig. 6. (A) Authors' impact by H index of scientific publication on coumarins and their derivatives used as antidepressants from 1996 to 2022. (B) An overlay visualisation of bibliographic coupling and authors of the scientific publications on coumarins and coumarins derivatives used as antidepressants from 1996 to 2022.

associated with research on the antidepressant effects of coumarins and their derivatives.

3.4.2.1. Global annual scientific publications and average citations per year. Between 1996 and 2022, covering more than two decades, the first rise in scientific published research was recorded in 2007, and the second in 2012 (Fig. 5A). However, the post-COVID-19 era - 2021 (Lockee, 2021) the highest number of publications (6) was produced. This observation is also affirmed by Carneiro et al. (2021). The impact of the of the pandemic on stress levels, depression, and anxiety in 2020 could have significantly impacted this spike in publications. There were no publications in some years. Furthermore, it is evident that coumarins and their derivatives are yet to be thoroughly explored for their antidepressant effects. Henceforth, there may be a positive research publication growth. The average citations per year surge for 2012 (Fig. 5B), appears to coincide with the increase in annual production in the same year (Fig. 5A). However, the post pandemic increase publication did not tally with citations. This observation may be due to delayed publication rate.

3.4.2.2. Global prominent authors. The number of publications a researcher has published and the number of times each work has been cited are used to determine the H-index. Bhatti R., Kaur A., and Singh L. have the highest publications of three each (Fig. 6A). However, according to the VOSviewer analysis, Carotti A, Vilar S, and Wang F had only two publications each but had the highest number of citations, 36, 41, and 41, respectively. This is suggestive that visibility of publications is important for citations. Moreso, Fig. 6B shows that some of the recent

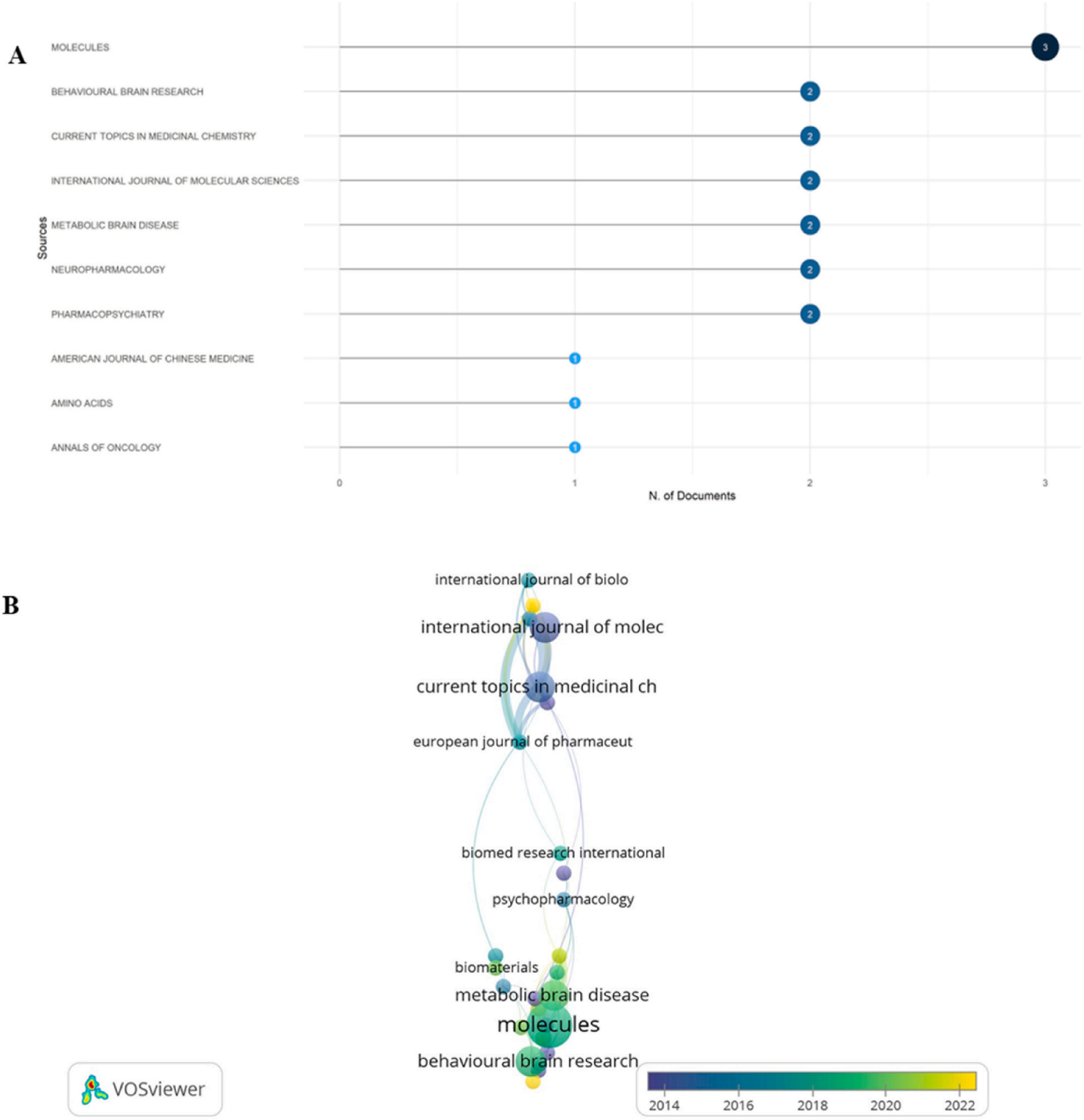


Fig. 7. (A) The top 10 most relevant journals associated with publications on the antidepressant effects of coumarins and their derivatives. (B) The most relevant journals associated with publications on the antidepressant effects of coumarins and their derivatives.

publications are from Bhatti R, and Apweiler M as indicated on the year scale based on the colour codes.

3.4.2.3. Global core journals: journal name. The most frequently cited journal is Molecules, an open-access publication, which reveals that the frequency of citations (Fig. 7A) is impacted by the journal's accessibility. The subscription-only journal Annals of Oncology received the fewest citations (Fig. 7A). Although citation analysis does not assess the level of scientific quality, it demonstrates the significance of the publication(s) (White-Gibson et al., 2019). The journal 'Molecules' (impact factor = 4.927, 2022) had the highest publication of 12, followed by Behaviour Brain Research (IF=3.352, 2022). The bibliographic coupling with source (journal) was conducted using the defined set: a minimum number of documents from a journal was set at one with a zero number of citations because of the recent 2022 publications. Based on VOSviewer analysis, Molecules and The Current Journal of Molecular Neuroscience, Experimental Brain Research and Bioorganic Chemistry are the trending journals (Fig. 7B).

3.4.2.4. Bibliometric participation among countries. The publications on

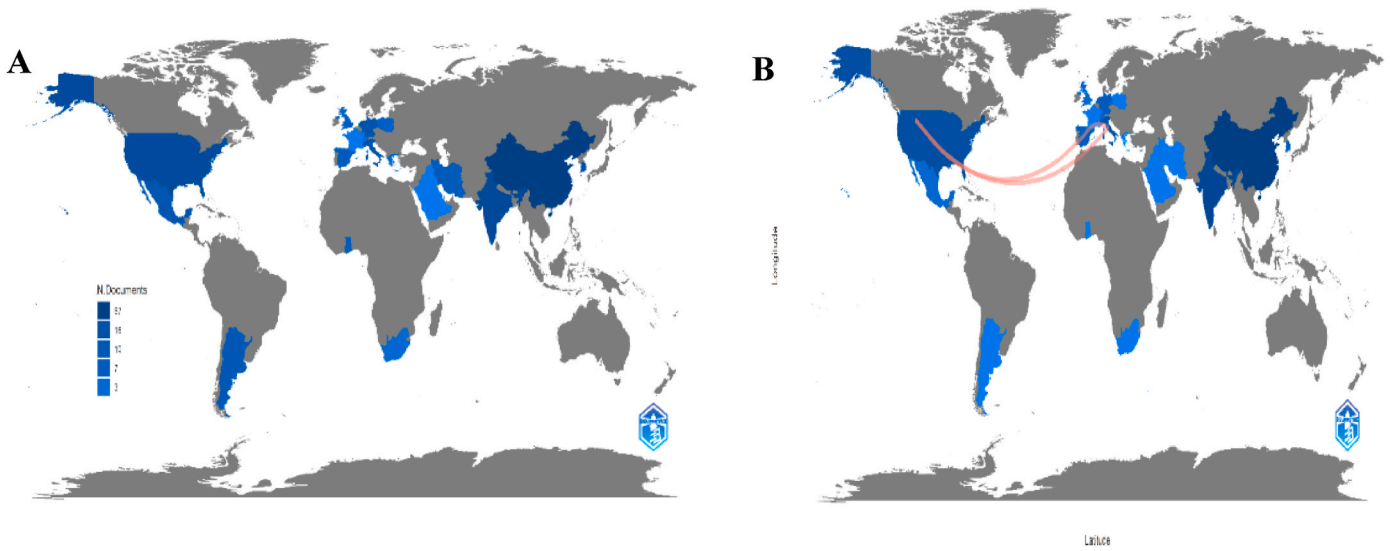


Fig. 8. (A) Geographical country scientific production ranking from 1996 to 2022. (B) Geographical country collaboration map from 1996 to 2022. The colour of the countries on the map (A) represents the number of documents signified on the scale bar.

Table 4
World collaboration frequency on the antidepressant effects of coumarins and their derivatives from 1996 to 2022.

Country 1	Country 2	Frequency
China	Hong Kong	1
China	Switzerland	1
China	United States of America	1
Germany	Spain	1
Germany	Switzerland	1
Ghana	United Kingdom	1
Italy	France	1
Italy	Greece	1
Italy	Spain	2
USA	Italy	2
USA	Spain	2
USA	United Kingdom	1

the antidepressant effect of coumarins and their derivatives originated from all continents, with exception of Australia and Antarctica (Fig. 8A). Considering that depression is a global disease (WHO, 2022), it may be misleading to conclude that Australia and Antarctica are not affected. The zero records on publications may be a result of a lack of documentation or perhaps a low prevalence frequency of the subject matter. The latter is reasonable for Australia as studies on the continent's depression rate recorded a low occurence (Stanton et al., 2020) and only 10% of the habitants were reported to have depression-like symptoms (ABS, 2017–2018). Comparatively speaking, countries in North America and Europe collaborate more than any other continents (Fig. 8B and Table 4).

The highest frequency (2) of collaboration was between USA and Italy; USA and Spain; as well as Italy and Spain. China also has a collaboration frequency of one with USA, Switzerland, Hong Kong, and

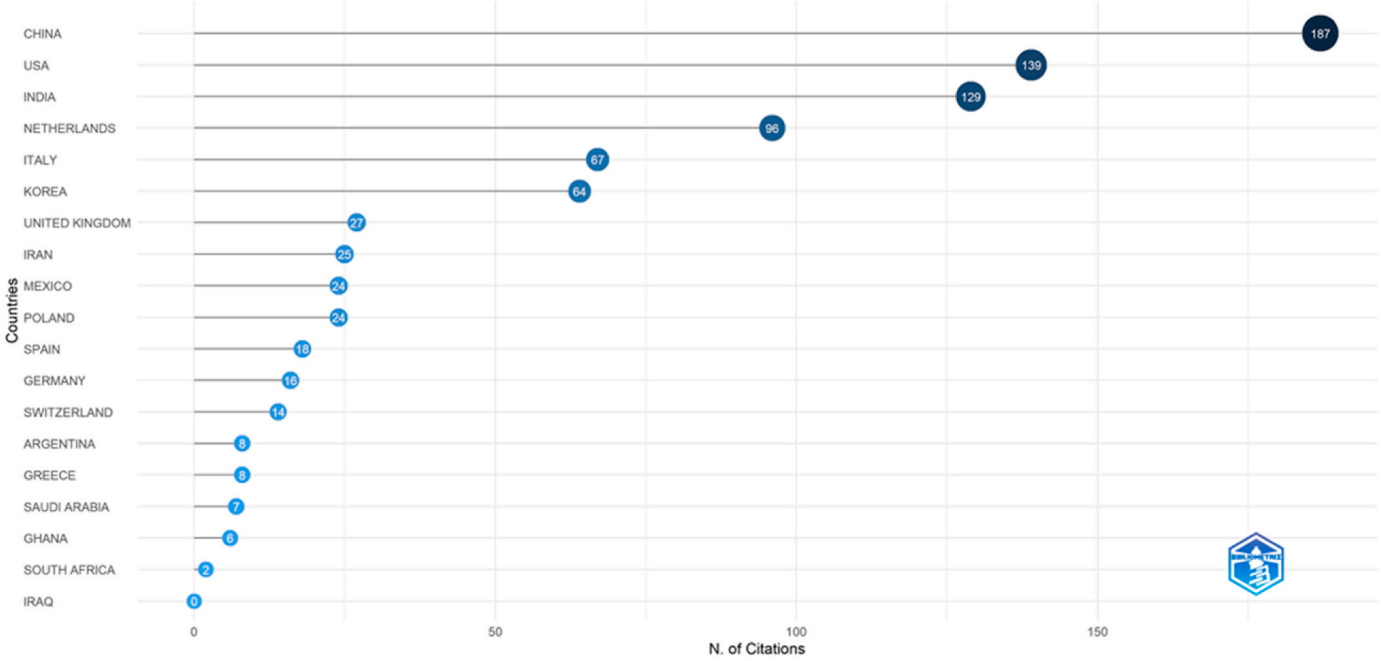


Fig. 9. Most cited countries from publications on the antidepressant effects of coumarins and their derivatives.

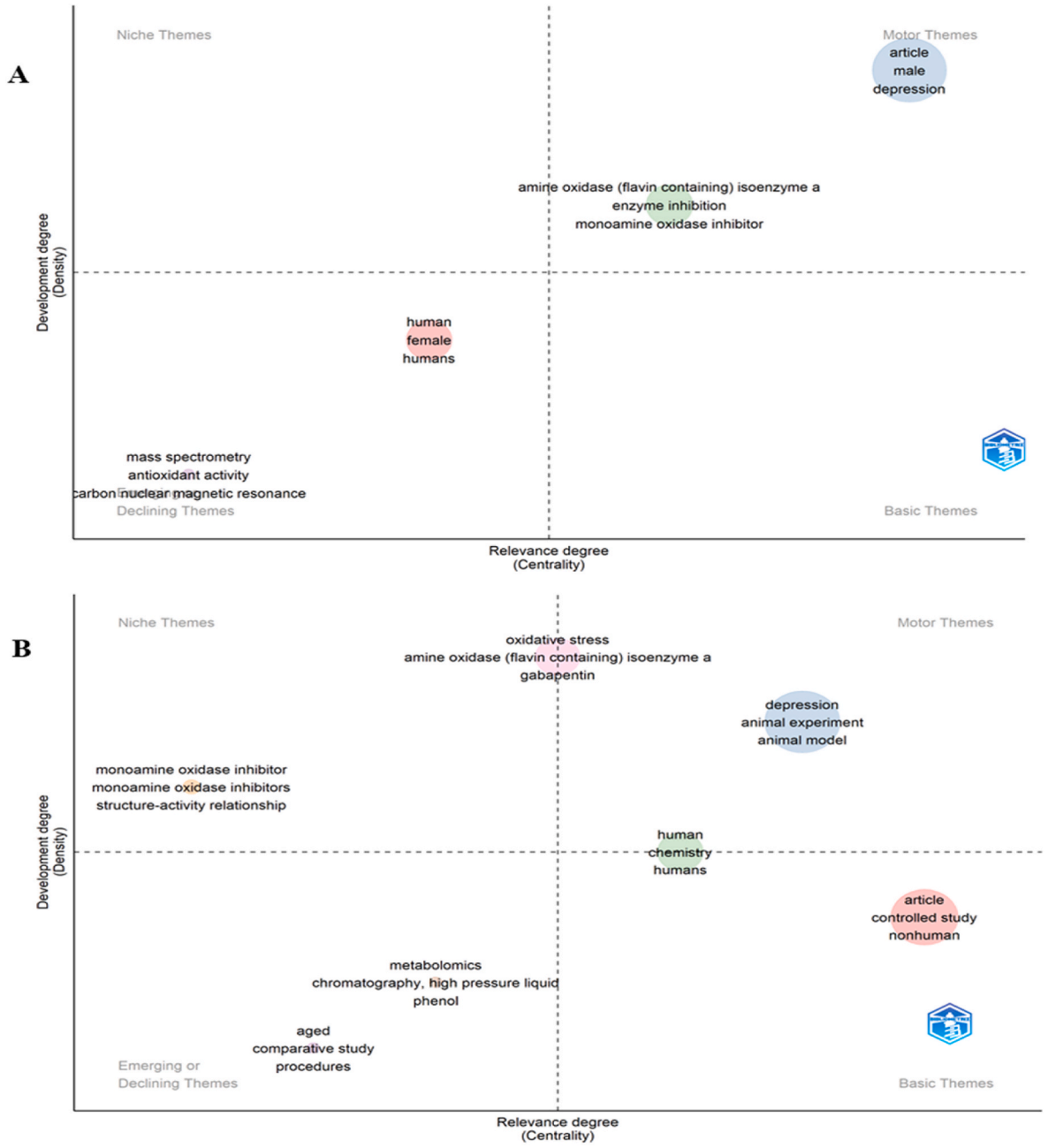


Fig. 10. (A) Thematic evolution map and (B) structure and patterns based on the co-occurrence of publications terms used in the antidepressant activities of coumarins and their derivatives articles.

India (Table 4). There is a very low collaboration frequency with any African country. In Africa, there are several reports on the antidepressant potentials of some indigenous medicinal plants with diverse phytochemicals including coumarins (Stafford et al., 2008; Manganyi et al., 2021; Bonokwane et al., 2022).

China (87) has the highest number of publications, while France, Iraq and Saudi Arabia had the least (1) (Table 4). China, India, the United States of America, and South Korea, are the top publishing nations (Table 4) with an average frequency above 20. China may be topping the publication list because several Chinese traditional medicine have been reported to exert antidepressant effects.

The most cited countries were China, USA, India, Netherlands, Italy, Korea, United Kingdom, Iran, Mexico, and Poland (Fig. 9). This order does not correlate with the top publishing countries (Table 4), it may be deduced that other factors such as availability of journals, source of information may have influenced this disparity. It is also possible that other Asian or a non-English speaking country could have also topped the chat but for the inclusion criteria that focused on publications written in English (Fig. 1).

3.4.2.5. Research thematic evolution. In the first thematic evolutionary trend map (1996–2017), there were no basic and niche themes (Fig. 10A). This could imply that in the early period of this timeline, the themes were not well-established. However, in the second map covering (2018–2022) (Fig. 10A), they were basic and niche themes, and the second thematic map clearly places 'article', 'controlled study' and 'nonhuman' in the basic theme's quadrant. Even though this is an indication of the importance of the themes, the research output is not substantial. The second thematic map (Fig. 10B), 'monoamine oxidase inhibitor(s)' and 'structure-activity relationship' are in the niche

themes, which implies that these are strongly developed themes, but with marginal importance for the field. Thus, both themes are peripheral topics. The motor or driving themes are the current research field patterns and well developed; and include 'depression', 'animal experiment', 'animal model' and 'human'. Although, there were some borderline themes 'chemistry', oxidative stress' which may eventually evolve completely to the motor themes. Likewise, 'article' evolved from motor to basic themes (Fig. 10A). Indeed, metabolomics in this field of study is an emerging theme, while certain procedures e.g., psychoanalytic theory to biological approaches are declining due to advancement in research.

4. Conclusion

Plant-derived coumarins could be used to develop potent antidepressant drugs. Coumarins and their derivatives are potential treatments for depression by targeting different pathways which are not mutually exclusive. However, the inflammatory (cytokines modulation), neurotrophic pathway (via BDNF activation), neuroinflammation (brain-gut-microbiome colony restoration) are not completely understood. Among the 31 reported coumarins and their derivatives, scopoletin, psoralen, 7-hydroxycoumarin, meranzin hydrate, osthole, esculetin/umbelliferone are among the most studied coumarins with antidepressant effects. Meranzin hydrate is presently the only coumarin derivative that is implicated in brain-gut-microbiota antidepressant pathway. Plant-based food/diet and lifestyle are two key factors that could help in enhancing the production of neurotransmitters. Despite the promising antidepressant effects of some coumarins and their derivatives, the effectiveness and safety of several more are yet to be fully investigated. In addition, there is a need for more colloborations among researchers in the different continents to fully understand the mechanisms, potential side effects and eventually identify the appropriate coumarin(s) to investigate in human clinical trials.

Funding

This research was financially supported by the National Research Foundation (NRF, UID 129 870) Pretoria, South Africa and the South African Medical Research Council Self-initiated funding. We appreciate the additional financial support provided by the North-West University, South Africa.

Declaration of competing interest

We hereby declare no conflict of interest with regards to this review. The NRF had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the chapter, or in the decision to publish the results.

Data availability

Data will be made available on request.

Acknowledgments

The authors are grateful to the Indigenous Knowledge Systems Centre, Faculty of Natural and Agricultural Sciences, North-West University, Mmabatho, South Africa and Preclinical Drug Development Platform, Faculty of Health Sciences, North-West University, Potchefstroom, South Africa for the provision of the postdoctoral research fellowship. We thank the School of Life Science, University of KwaZulu-Natal for institutional support.

References

Abourashed, E.A., 2018. Review of discovery and development of neuroprotective agents from natural products. J. Nat. Prod. 81, 1917–1918.
ABS, 2017-2018. Mental Health Australian Bureau of Statistics.
Adu-Nti, F., Gao, X., Wu, J.-M., Li, J., Iqbal, J., Ahmad, R., Ma, X.-M., 2021. Osthole ameliorates estrogen deficiency-induced cognitive impairment in female mice. Front. Pharmacol. 12, 641909.
Akwu, N.A., Naidoo, Y., Singh, M., 2019. Cytogenotoxic and biological evaluation of the aqueous extracts of *Grewia lasiocarpa*: an *Allium cepa* assay. South Afr. J. Bot. 125, 371–380.
Alqasoumi, S., 2012. Anxiolytic effect of *Ferula assafoetida* L. in rodents. J. Pharmacogn. Phytother. 4, 86–90.
Alqasoumi, S., Al-Dosari, M., Al-Howiriny, T., Al-Yahya, M., Al-Mofleh, I., Rafatullah, S., 2011. Gastric antiulcer activity of a pungent spice *Ferula assafoetida* in rats. FARMACIA 59, 750–759.
Amoateng, P., Kukuia, K.K.E., Mensah, J.A., Osei-Safo, D., Adjei, S., Eklemet, A.A., Vinyo, E.A., Karikari, T.K., 2018. An extract of *Synedrella nodiflora* (L) Gaertn exhibits antidepressant properties through monoaminergic mechanisms. Metab. Brain Dis. 33, 1359–1368.
Apweiler, M., Streyczek, J., Saliba, S.W., Collado, J.A., Hurrle, T., Gräßle, S., Muñoz, E., Normann, C., Hellwig, S., Bräse, S., 2022. Functional selectivity of coumarin derivates acting via GPR55 in neuroinflammation. Int. J. Mol. Sci. 23, 959.
Aria, M., Cuccurullo, C., 2017. Bibliometrix: an R-tool for comprehensive science mapping analysis. J. Informetr. 11, 959–975.
Askar, S.J., 2019. Study the phytochemical analysis and modulatory effects of hydroalcoholic extract of *Morus* plant leaves on mental depressive disorder. Indian J. Forensic Med. Toxicol. 13, 1348–1353.
Behl, T., Rana, T., Alotaibi, G.H., Shamsuzzaman, M., Naqvi, M., Sehgal, A., Singh, S., Sharma, N., Almoshari, Y., Abdellatif, A.A., 2022. Polyphenols inhibiting MAPK signalling pathway mediated oxidative stress and inflammation in depression. Biomed. Pharmacother. 146, 112545.
Belmaker, R.H., Agam, G., 2008. Major depressive disorder. N. Engl. J. Med. 358, 55–68.
Bester, E., Petzer, A., Petzer, J.P., 2022. Coumarin derivatives as inhibitors of d-amino acid oxidase and monoamine oxidase. Bioorg. Chem. 123, 105791.
Bhattarai, N., Kumbhar, A.A., Pokharel, Y.R., Yadav, P.N., 2021. Anticancer potential of coumarin and its derivatives. Mini Rev. Med. Chem. 21, 2996–3029.
Björkholm, C., Monteggia, L.M., 2016. BDNF–a key transducer of antidepressant effects. Neuropharmacology 102, 72–79.
Bonokwane, M.B., Lekhooa, M., Struwig, M., Aremu, A.O., 2022. Antidepressant effects of South African plants: an appraisal of ethnobotanical surveys, ethnopharmacological and phytochemical studies. Front. Pharmacol. 13, 895286.
Born, S., Api, A., Ford, R., Lefever, F., Hawkins, D., 2003. Comparative metabolism and kinetics of coumarin in mice and rats. Food Chem. Toxicol. 41, 247–258.
Bovell-Benjamin, A.C., Roberts, J., 2016. Naturally occurring toxicants: Presence in selected commonly consumed fruits. In: Prakash, V., Martín-Belloso, O., Keener, L., Astley, S., Braun, S., McMahon, H., Lelieveld (Eds.), Regulating Safety of Traditional and Ethnic Foods. Academic Pres, San Diego, USA, pp. 247–282.
Buckingham, J., Macdonald, F., Bradley, H., 1994. Dictionary of Natural Products. Chapman and Hall, London, United Kingdom.
Budzynska, B., Skalicka-Wozniak, K., Kruk-Slomka, M., Wydrzynska-Kuzma, M., Biala, G., 2016. *In vivo* modulation of the behavioral effects of nicotine by the coumarins xanthotoxin, bergapten, and umbelliferone. Psychopharmacology 233, 2289–2300.
Bukhari, I., Dar, A., 2013. Behavioral profile of *Hypericum perforatum* (St. John's Wort) extract. A comparison with standard antidepressants in animal models of depression. Eur. Rev. Med. Pharmacol. Sci. 17, 1082–1089.
Byrden, T., 1995. The Elucidation of the Mode of Action of Coumarin and Some Specified Derivatives. Doctoral dissertation, Dublin City University Dublin, Ireland.
Capra, J.C., Cunha, M.P., Machado, D.G., Zomkowski, A.D., Mendes, B.G., Santos, A.R.S., Pizzolatti, M.G., Rodrigues, A.L.S., 2010. Antidepressant-like effect of scopoletin, a coumarin isolated from *Polygala sabulosa* (Polygalaceae) in mice: evidence for the involvement of monoaminergic systems. Eur. J. Pharmacol. 643, 232–238.
Carneiro, A., Matos, M.J., Uriarte, E., Santana, L., 2021. Trending topics on coumarin and its derivatives in 2020. Molecules 26, 501.
Carotti, A., Carrieri, A., Chimichi, S., Boccalini, M., Cosimelli, B., Gnerre, C., Carotti, A., Carrupt, P.-A., Testa, B., 2002. Natural and synthetic geiparvarins are strong and selective MAO-B inhibitors. Synthesis and SAR studies. Bioorg. Med. Chem. Lett 12, 3551–3555.
Catto, M., Nicolotti, O., Leonetti, F., Carotti, A., Favia, A.D., Soto-Otero, R., Méndez-Álvarez, E., Carotti, A., 2006. Structural insights into monoamine oxidase inhibitory potency and selectivity of 7-substituted coumarins from ligand-and target-based approaches. J. Med. Chem. 49, 4912–4925.
Chen, H.-F., Zhang, W.-G., Yuan, J.-B., Li, Y.-G., Yang, S.-L., Yang, W.-L., 2012. Simultaneous quantification of polymethoxylated flavones and coumarins in *Fructus aurantii* and *Fructus aurantii immaturus* using HPLC–ESI-MS/MS. J. Pharmaceut. Biomed. Anal. 59, 90–95.
Chen, P., Hei, M., Kong, L., Liu, Y., Yang, Y., Mu, H., Zhang, X., Zhao, S., Duan, J., 2019. One water-soluble polysaccharide from *Ginkgo biloba* leaves with antidepressant activities via modulation of the gut microbiome. Food Funct. 10, 8161–8171.
Chen, Q., Xiao, E.Y., Goldman, A.L., Bharadwaj, R., Healy, K., Zoltick, B., Das, S., Berman, K., Weinberger, D.R., Mattay, V.S., 2015. W1. Rs362691 Polymorphism in RELN gene modulates the detrimental effect of Alzheimer's disease risk genes on hippocampal function. Neuropsychopharmacology 40, S443–S611.

Chen, Y., Kong, L.-D., Xia, X., Kung, H.-F., Zhang, L., 2005. Behavioral and biochemical studies of total furocoumarins from seeds of *Psoralea corylifolia* in the forced swimming test in mice. J. Ethnopharmacol. 96, 451–459.
Cheng, D., Murtaza, G., Ma, S., Li, L., Li, X., Tian, F., Zheng, J., Lu, Y., 2017. *In silico* prediction of the anti-depression mechanism of a herbal formula (Tiansi liquid) containing *Morinda officinalis* and *Cuscuta chinensis*. Molecules 22, 1614.
Chong, P.P., Chin, V.K., Looi, C.Y., Wong, W.F., Madhavan, P., Yong, V.C., 2019. The microbiome and irritable bowel syndrome–a review on the pathophysiology, current research and future therapy. Front. Microbiol. 10, 1136.
Cobo, M.J., Martínez, M.-Á., Gutiérrez-Salcedo, M., Fujita, H., Herrera-Viedma, E., 2015. 25 years at knowledge-based systems: a bibliometric analysis. Knowl. Base Syst. 80, 3–13.
Delogu, G.L., Serra, S., Quezada, E., Uriarte, E., Vilar, S., Tatonetti, N.P., Viña, D., 2014. Monoamine oxidase (MAO) inhibitory activity: 3-phenylcoumarins versus 4-hydroxy-3-phenylcoumarins. ChemMedChem 9, 1672–1676.
Dhailappan, A., Samiappan, S., 2022. Impact of diet on neurotransmitters. In: Rajagopal, S., Ramachandran, S., Sundararaman, G., Gadde Venkata, S. (Eds.), Role of Nutrients in Neurological Disorders. Springer, Singapore, pp. 363–383.
Dhiman, P., Malik, N., Khatkar, A., 2018. Exploration of umbelliferone based derivatives as potent MAO inhibitors: dry vs. wet lab evaluation. Curr. Top. Med. Chem. 18, 1857–1871.
Dikmen, S.S., Bombardier, C.H., Machamer, J.E., Fann, J.R., Temkin, N.R., 2004. Natural history of depression in traumatic brain injury. Arch. Phys. Med. Rehabil. 85, 1457–1464.
Dinan, T.G., Cryan, J.F., 2017. Brain-gut-microbiota axis and mental health. Psychosom. Med. 79, 920–926.
Dreyer, D.L., Lee, A., 1972. Extractives of *Geijera parviflora*. Phytochemistry 11, 763–767.
Duns, P., 2013. Dublin Region Public Analyst's Laboratory. Feidhmeannas Seirbhise Slainte Health Service Executive Dublin, pp. 1–72.
Egan, D., O'kennedy, R., Moran, E., Cox, D., Prosser, E., Thornes, R.D., 1990. The pharmacology, metabolism, analysis, and applications of coumarin and coumarin-related compounds. Drug Metabol. Rev. 22, 503–529.
Erdogan Orhan, I., Ozan Gulcan, H., 2015. Coumarins: auspicious cholinesterase and monoamine oxidase inhibitors. Curr. Top. Med. Chem. 15, 1673–1682.
Escudero, G.E., Laino, C.H., Echeverría, G.A., Piro, O.E., Martini, N., Rodríguez, A.N., Medina, J.J.M., Tévez, L.L.L., Ferrer, E.G., Williams, P.A., 2016. Improving the antidepressant action and the bioavailability of sertraline by co-crystallization with coumarin 3-carboxylate. Structural determination. Chem. Biol. Interact. 249, 46–55.
Estévez-Braun, A., González, A.G., 1997. Coumarins. Nat. Prod. Rep. 14, 465–475.
Fiedorowicz, J.G., Swartz, K.L., 2004. The role of monoamine oxidase inhibitors in current psychiatric practice. J. Psychiatr. Pract. 10, 239.
Fries, G.R., Saldana, V.A., Finnstein, J., Rein, T., 2023. Molecular pathways of major depressive disorder converge on the synapse. Mol. Psychiatr. 28, 284–297.
Gabriela, G.-C., Javier, A.-A.F., Elisa, V.-A., Gonzalo, V.-P., Herlinda, B.-J., 2012. Antidepressant-like effect of *Tagetes lucida* Cav. extract in rats: involvement of the serotonergic system. Am. J. Chin. Med. 40, 753–768.
Gnerre, C., Catto, M., Leonetti, F., Weber, P., Carrupt, P.-A., Altomare, C., Carotti, A., Testa, B., 2000. Inhibition of monoamine oxidases by functionalized coumarin derivatives: biological activities, QSARs, and 3D-QSARs. J. Med. Chem. 43, 4747–4758.
Gomez-Pinilla, F., Nguyen, T.T., 2012. Natural mood foods: the actions of polyphenols against psychiatric and cognitive disorders. Nutr. Neurosci. 15, 127–133.
Gu, X., Zhou, Y., Wu, X., Wang, F., Zhang, C.-Y., Du, C., Shen, L., Chen, X., Shi, J., Liu, C., 2014. Antidepressant-like effects of auraptenol in mice. Sci. Rep. 4, 4433.
Guglielmi, P., Carradori, S., D'Agostino, I., Campestre, C., Petzer, J.P., 2022. An updated patent review on monoamine oxidase (MAO) inhibitors. Expert Opin. Ther. Pat. 32, 849–883.
Guieu, B., Jourdan, J.-P., Dreneau, A., Willand, N., Rochais, C., Dallemagne, P., 2021. Desirable drug–drug interactions or when a matter of concern becomes a renewed therapeutic strategy. Drug Discov. Today 26, 315–328.
Hampel, H., Berger, C., Kuss, H.-J., Müller-Spahn, F., 1996. Unstable anticoagulation in the course of amitriptyline treatment. Pharmacopsychiatry 29, 33–37.
Hasan, M.K., Ara, I., Mondal, M.S.A., Kabir, Y., 2021. Phytochemistry, pharmacological activity, and potential health benefits of *Glycyrrhiza glabra*. Heliyon 7, e07240.
Hassanein, E.H., Sayed, A.M., Hussein, O.E., Mahmoud, A.M., 2020. Coumarins as modulators of the Keap1/Nrf2/ARE signaling pathway. Oxid. Med. Cell. Longev. 2020 Article ID 1675957.
Heghes, S.C., Vostinaru, O., Mogosan, C., Miere, D., Iuga, C.A., Filip, L., 2022. Safety profile of nutraceuticals rich in coumarins: an update. Front. Pharmacol. 13, 48.
Herbet, M., Widelski, J., Piątkowska-Chmiel, I., Pawłowski, K., Dymek, A., Mroczek, T., 2022. Amaryllidaceae, Lycopodiaceae alkaloids and coumarins-a comparative assessment of safety and pharmacological activity. J. Clin. Med. 11, 4291.
Hernández-Vázquez, L., Cassani, J., Heyerdahl-Viau, I., Martínez-Casares, R.M., Luna, H., Dorantes-Barrón, A.M., Arrieta-Báez, D., Estrada-Reyes, R., 2022. Recovery of naringin-rich flavonoid extracts from agroresidues with anxiolytic and antidepressant-like effects in mice. Molecules 27, 8507.
Hunter, K., Poel, K., Pennington, S., Bindseil, I., Banerji, S., Leonard, J., Wang, G.S., 2022. Trends of prescription psychotropic medication exposures in pediatric patients, 2009–2018. Clin. Toxicol. 60, 243–251.
Irvine, M.W., Costa, B.M., Volianskis, A., Fang, G., Ceolin, L., Collingridge, G.L., Monaghan, D.T., Jane, D.E., 2012. Coumarin-3-carboxylic acid derivatives as potentiators and inhibitors of recombinant and native N-methyl-D-aspartate receptors. Neurochem. Int. 61, 593–600.
Jameel, E., Umar, T., Kumar, J., Hoda, N., 2016. Coumarin: a privileged scaffold for the design and development of antineurodegenerative agents. Chem. Biol. Drug Des. 87, 21–38.
Jang, J.H., Park, J.E., Han, J.S., 2020. Scopoletin increases glucose uptake through activation of PI3K and AMPK signaling pathway and improves insulin sensitivity in 3T3-L1 cells. Nutr. Res. 74, 52–61.
Jeong, S.H., Han, X.H., Hong, S.S., Hwang, J.S., Hwang, J.H., Lee, D., Lee, M.K., Ro, J.S., Hwang, B.Y., 2006. Monoamine oxidase inhibitory coumarins from the aerial parts of *Dictamnus albus*. Arch Pharm. Res. (Seoul) 29, 1119–1124.
Jerris, P.J., Smith III, A.B., 1981. Synthesis and configurational assignment of geiparvarin: a novel antitumor agent. J. Org. Chem. 46, 577–585.
Jiang, Y., Zou, D., Li, Y., Gu, S., Dong, J., Ma, X., Xu, S., Wang, F., Huang, J.H., 2022. Monoamine neurotransmitters control basic emotions and affect major depressive disorders. Pharmaceuticals 15, 1203.
Jo, Y.S., Huong, D.T.L., Bae, K.H., Lee, M.K., Kim, Y.H., 2002. Monoamine oxidase inhibitory coumarin from *Zanthoxylum schinifolium*. Planta Med. 68, 84–85.
Kaczmarczyk, M., Regen, F., Heuser, I., Bajbouj, M., Hellmann-Regen, J., 2020. Inhibition of monoamine oxidase activity by repetitive transcranial magnetic stimulation: implications for inter-train interval and frequency. Eur. Arch. Psychiatr. Clin. Neurosci. 270, 119–126.
Kallitsakis, M.G., Carotti, A., Catto, M., Peperidou, A., Hadjipavlou-Litina, D.J., Litinas, K.E., 2017. Synthesis and biological evaluation of novel hybrid molecules containing purine, coumarin and isoxazoline or isoxazole moieties. Open Med. Chem. J. 11, 196.
Kaur, A., Singh, L., Singh, N., Bhatti, M.S., Bhatti, R., 2019. Ameliorative effect of imperatorin in chemically induced fibromyalgia: role of NMDA/NFkB mediated downstream signaling. Biochem. Pharmacol. 166, 56–69.
Kenda, M., Kočevar Glavač, N., Nagy, M., Sollner Dolenc, M., 2022. Medicinal plants used for anxiety, depression, or stress treatment: an update. Molecules 27, 6021.
Khilya, O., Shablykina, O., Frasinyuk, M., Ishchenko, V., Khilya, V., 2005. 3-(2-Pyridyl) coumarins. Chem. Nat. Compd. 41, 523–528.
Kılıç, C.S., 2022. Herbal coumarins in healthcare. In: Mandal, S.C., Nayak, A.K., Dhara, A.K. (Eds.), Herbal Biomolecules in Healthcare Applications. Academic Press, pp. 363–380.
Kong, L.D., Tan, R.X., Woo, A.Y.H., Cheng, C.H.K., 2001. Inhibition of rat brain monoamine oxidase activities by psoralen and isopsoralen: implications for the treatment of affective disorders. Pharmacol. Toxicol. 88, 75–80.
Korczyn, A.D., Halperin, I., 2009. Depression and dementia. J. Neurol. Sci. 283, 139–142.
Kostova, I., 2005. Synthetic and natural coumarins as cytotoxic agents. Curr. Med. Chem. Anti-Cancer Agents 5, 29–46.
Koyiparambath, V.P., Prayaga Rajappan, K., Rangarajan, T., Al-Sehemi, A.G., Pannipara, M., Bhaskar, V., Nair, A.S., Sudevan, S.T., Kumar, S., Mathew, B., 2021. Deciphering the detailed structure–activity relationship of coumarins as monoamine oxidase enzyme inhibitors—an updated review. Chem. Biol. Drug Des. 98, 655–673.
Latimer, D., Cornett, E.M., 2023. Antidepressants, antiparkinson drugs. In **Abd-Elsayed**, A. In: Advanced Anesthesia Review. Oxford University Press, p. 126.
Lee, A., Sun, Y., Lin, T., Song, N.-J., Mason, M.L., Leung, J.H., Kowdley, D., Wall, J., Brunetti, A., Fitzgerald, J., 2020a. Amino acid-based compound activates atypical PKC and leptin receptor pathways to improve glycemia and anxiety like behavior in diabetic mice. Biomaterials 239, 119839.
Lee, B., Yeom, M., Shim, I., Lee, H., Hahm, D.-H., 2020b. Umbelliferone modulates depression-like symptoms by altering monoamines in a rat post-traumatic stress disorder model. J. Nat. Med. 74, 377–386.
Lee, H.W., Ryu, H.W., Kang, M.-G., Park, D., Lee, H., Shin, H.M., Oh, S.-R., Kim, H., 2017. Potent inhibition of monoamine oxidase A by decursin from *Angelica gigas* Nakai and by wogonin from *Scutellaria baicalensis* Georgi. Int. J. Biol. Macromol. 97, 598–605.
Lee, S.-J., Chung, H.-Y., Lee, I.-K., Oh, S.-U., Yoo, I.-D., 2000. Phenolics with inhibitory activity on mouse brain monoamine oxidase (MAO) from whole parts of *Artemisia vulgaris* L (Mugwort). Food Sci. Biotechnol. 9, 179–182.
Lee, S.Y., Park, M.C., 2000. Perceived stressful life events, coping style, social support and depressive symptoms of the functional dyspepsia patients. J. Korean Neuropsychiatr. Assoc. 39, 351.
Liang, F., Xu, Q., Jiang, M., Feng, R., Jiang, S., Yuan, B., Xu, S., Wu, T., Wang, F., Huang, J.H., 2021. Emotion induced monoamine neuromodulator release affects functional neurological disorders. Front. Cell Dev. Biol. 9, 633048.
Liang, J., Shu, L., Luo, Z., Liu, P., Yang, M., Tan, C., 2002. Preliminary clinical effectiveness of *Morinda offcinalis* water extract in the treatment of depression. J. Chinese Mat. Med. 27, 75–78.
Liu, H., Zhang, X., Shi, P., Yuan, J., Jia, Q., Pi, C., Chen, T., Xiong, L., Chen, J., Tang, J., 2023. α7 Nicotinic acetylcholine receptor: a key receptor in the cholinergic anti-inflammatory pathway exerting an antidepressant effect. J. Neuroinflammation 20, 84.
Liu, X., Zhou, J., Zhang, T., Chen, K., Xu, M., Wu, L., Liu, J., Huang, Y., Nie, B., Shen, X., 2021. Meranzin hydrate elicits antidepressant effects and restores reward circuitry. Behav. Brain Res. 398, 112898.
Lockee, B.B., 2021. Online education in the post-COVID era. Nat. Electron. 4, 5–6.
Madeiro, S.A., Borges, N.H., Souto, A.L., de Figueiredo, P.T., Siqueira-Junior, J.P., Tavares, J.F., 2017. Modulation of the antibiotic activity against multidrug resistant strains of coumarins isolated from Rutaceae species. Microb. Pathog. 104, 151–154.
Mandal, P.K., Gaur, S., Roy, R.G., Samkaria, A., Ingole, R., Goel, A., 2022. Schizophrenia, bipolar and major depressive disorders: overview of clinical features, neurotransmitter alterations, pharmacological interventions, and impact of oxidative stress in the disease process. ACS Chem. Neurosci. 13, 2784–2802.
Manganyi, M.C., Bezuidenhout, C.C., Regnier, T., Ateba, C.N., 2021. A chewable cure "kanna": biological and pharmaceutical properties of *Sceletium tortuosum*. Molecules 26, 2557.
Mangiatordi, G.F., Alberga, D., Pisani, L., Gadaleta, D., Trisciuzzi, D., Farina, R., Carotti, A., Lattanzi, G., Catto, M., Nicolotti, O., 2017. A rational approach to

elucidate human monoamine oxidase molecular selectivity. Eur. J. Pharmaceut. Sci. 101, 90–99.
Marazziti, D., Carlini, M., Dell'Osso, L., 2012. Treatment strategies of obsessive-compulsive disorder and panic disorder/agoraphobia. Curr. Top. Med. Chem. 12, 238–253.
Martelli, A., Breschi, M.C., Calderone, V., 2009. Pharmacodynamic hybrids coupling established cardiovascular mechanisms of action with additional nitric oxide releasing properties. Curr. Pharmaceut. Des. 15, 614–636.
Matés, J.M., Pérez-Gómez, C., De Castro, I.N., 1999. Antioxidant enzymes and human diseases. Clin. Biochem. 32, 595–603.
Matos, M.J., Herrera Ibata, D.M., Uriarte, E., Viña, D., 2020. Coumarin-rasagiline hybrids as potent and selective hMAO-B inhibitors, antioxidants, and neuroprotective agents. ChemMedChem 15, 532–538.
Mattsson, B., Mjörndal, T., Oreland, L., Perris, C., Persson, S., 1972. Monoamine oxidase (MAO) and catechol methyltransferase (COMT) in affective disturbances. Nordisk Psykiatrisk tidsskrift. Nord. J. Psychiatr. 26, 359–360.
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34.
Moloney, R.D., Desbonnet, L., Clarke, G., Dinan, T.G., Cryan, J.F., 2014. The microbiome: stress, health and disease. Mamm. Genome 25, 49–74.
Monadi, T., Azadbakht, M., Ahmadi, A., Chabra, A., 2021. A Comprehensive review on the ethnopharmacology, phytochemistry, pharmacology, and toxicology of the *Mandragora* genus; from folk medicine to modern medicine. Curr. Pharmaceut. Des. 27, 3609–3637.
Monastero, R., Camarda, R., Camarda, C., 2007. Potential drug-drug interaction between duloxetine and acenocoumarol in a patient with Alzheimer's disease. Clin. Therapeut. 29, 2706–2709.
Monsef-Esfahani, H.R., Amini, M., Goodarzi, N., Saiedmohammadi, F., Hajiaghaee, R., Faramarzi, M.A., Tofighi, Z., Ghahremani, M.H., 2013. Coumarin compounds of *Biebersteinia multifida* roots show potential anxiolytic effects in mice. Daru J. Pharm. Sci. 21, 51.
Murray, R.D.H., Méndez, J., Brown, S.A., 1982. In: Chichester (Ed.), The Natural Coumarins Occurrence, Chemistry and Biochemistry. John Wiley and Sons Ltd., New York, NY, USA.
Nabeel, Z., Jaber, Q.A.-H., Abdul-Rida, N.A., 2021. Novel benzo [f] coumarin derivatives as probable acetylcholinesterase inhibitors: synthesis, *in vitro*, and *in silico* studies for evaluation of their anti-AChE activity. Indonesian J. Chem. 22, 35–46.
Nekovarova, T., Yamamotova, A., Vales, K., Stuchlik, A., Fricova, J., Rokyta, R., 2014. Common mechanisms of pain and depression: are antidepressants also analgesics? Front. Behav. Neurosci. 8, 99.
Nie, K., Liu, L., Peng, L., Zhang, M., Zhang, C., Xiao, B., Xia, Z., Huang, W., 2022. Effects of meranzin hydrate on the LncRNA–miRNA–mRNA regulatory network in the hippocampus of a rat model of depression. J. Mol. Neurosci. 72, 910–922.
Nonen, S., Kato, M., Takekita, Y., Wakeno, M., Sakai, S., Serretti, A., Kinoshita, T., 2016. Polymorphism of rs3813034 in serotonin transporter gene SLC6A4 is associated with the selective serotonin and serotonin-norepinephrine reuptake inhibitor response in depressive disorder: sequencing analysis of: SLC6A4. J. Clin. Psychopharmacol. 36, 27–31.
Pacher, P., Kecskemeti, V., 2004. Trends in the development of new antidepressants. Is there a light at the end of the tunnel? Curr. Med. Chem. 11, 925–943.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br. Med. J. 372, n71.
Park, B.-K., Kim, Y.R., Kim, Y.H., Yang, C., Seo, C.-S., Jung, I.C., Jang, I.-S., Kim, S.-H., Lee, M.Y., 2018. Antidepressant-like effects of Gyejibokryeong-hwan in a mouse model of reserpine-induced depression. BioMed Res. Int. 2018.
Patel, S.S., Mahindroo, N., Udayabanu, M., 2016. *Urtica dioica* leaves modulates hippocampal smoothened-glioma associated oncogene-1 pathway and cognitive dysfunction in chronically stressed mice. Biomed. Pharmacother. 83, 676–686.
Pathak, A., K Srivastava, A., K Singour, P., Gouda, P., 2016. Synthetic and natural monoamine oxidase inhibitors as potential lead compounds for effective therapeutics. Cent. Nerv. Syst. Agents Med. Chem. 16, 81–97.
Patil, P.O., Bari, S.B., Firke, S.D., Deshmukh, P.K., Donda, S.T., Patil, D.A., 2013. A comprehensive review on synthesis and designing aspects of coumarin derivatives as monoamine oxidase inhibitors for depression and Alzheimer's disease. Bioorg. Med. Chem. 21, 2434–2450.
Porsolt, R., Bertin, A., Jalfre, M., 1977a. Behavioral despair in mice: a primary screening test for antidepressants. Arch. Int. Pharmacodyn. Ther. 229, 327–336.
Porsolt, R.D., Le Pichon, M., Jalfre, M., 1977b. Depression: a new animal model sensitive to antidepressant treatments. Nature 266, 730–732.
Porter, G.A., O'Connor, J.C., 2022. Brain-derived neurotrophic factor and inflammation in depression: pathogenic partners in crime? World J. Psychiatr. 12, 77.
Qin, T., Fang, F., Song, M., Li, R., Ma, Z., Ma, S., 2017. Umbelliferone reverses depression-like behavior in chronic unpredictable mild stress-induced rats by attenuating neuronal apoptosis via regulating ROCK/Akt pathway. Behav. Brain Res. 317, 147–156.
Ramsay, R., 2012. Monoamine oxidases: the biochemistry of the proteins as targets in medicinal chemistry and drug discovery. Curr. Top. Med. Chem. 12, 2189–2209.
Ramsay, R.R., Majekova, M., Medina, M., Valoti, M., 2016. Key targets for multi-target ligands designed to combat neurodegeneration. Front. Neurosci. 10, 375.
Ratanasavanh, D., Lamiable, D., Biour, M., Guedes, Y., Gersberg, M., Leutenegger, E., Riche, C., 1996. Metabolism and toxicity of coumarin on cultured human, rat, mouse and rabbit hepatocytes. Fund. Clin. Pharmacol. 10, 504–510.
Rehuman, N.A., Mathew, B., Jat, R.K., Nicolotti, O., Kim, H., 2020. A comprehensive review of monoamine oxidase-A inhibitors in their syntheses and potencies. Comb. Chem. High Throughput Screen. 23, 898–914.
Rodriguez-Enriquez, F., Costas-Lago, M.C., Besada, P., Alonso-Pena, M., Torres-Teran, I., Vina, D., Fontenla, J.Á., Sturlese, M., Moro, S., Quezada, E., 2020. Novel coumarin-pyridazine hybrids as selective MAO-B inhibitors for the Parkinson's disease therapy. Bioorg. Chem. 104, 104203.
Roohi, E., Jaafari, N., Hashemian, F., 2021. On inflammatory hypothesis of depression: what is the role of IL-6 in the middle of the chaos? J. Neuroinflammation 18, 1–15.
Sahni, T., Sharma, S., Verma, D., Kaur, P., 2021. Overview of coumarins and its derivatives: synthesis and biological activity. Lett. Org. Chem. 18, 880–902.
Sairam, K.V., Khar, R.K., Mukherjee, R., Jain, S.K., 2007. Three dimensional pharmacophore modelling of monoamine oxidase-A (MAO-A) inhibitors. Int. J. Mol. Sci. 8, 894–919.
Sarker, S.D., Nahar, L., 2017. Progress in the chemistry of naturally occurring coumarins. Prog. Chem. Org. Nat. Prod. 106, 241–304.
Sarwar, H., Rafiqi, S.I., Ahmad, S., Jinna, S., Khan, S.A., Karim, T., Qureshi, O., Zahid, Z. A., Elhai, J.D., Levine, J.C., 2022. Hyperinsulinemia associated depression. Clin. Med. Insights Endocrinol. Diabetes 15, 11795514221090244.
Sashidhara, K.V., Modukuri, R.K., Singh, S., Rao, K.B., Teja, G.A., Gupta, S., Shukla, S., 2015. Design and synthesis of new series of coumarin–aminopyran derivatives possessing potential anti-depressant-like activity. Bioorg. Med. Chem. Lett 25, 337–341.
Schurr, A., Livne, A., 1976. Differential inhibition of mitochondrial monoamine oxidase from brain by hashish components. Biochem. Pharmacol. 25, 1201–1203.
Sharma, M., Vyas, V.K., Bhatt, S., Ghate, M.D., 2022. Therapeutic potential of 4-substituted coumarins: a conspectus. Eur. J. Med. Chem. Rep., 100086
Shrivastava, A., Mittal, A., Khabiya, R., Choudhary, G., Darwhekar, G.N., 2022. Characteristics, biological activities, synthesis, and methods for the determination of brexpiprazole in different matrices. Curr. Pharmaceut. Anal. 18, 765–776.
Singh, L., Kaur, A., Garg, S., Bhatti, R., 2021. Skimmetin/osthole mitigates pain-depression dyad via inhibiting inflammatory and oxidative stress-mediated neurotransmitter dysregulation. Metab. Brain Dis. 36, 111–121.
Singh, L., Kaur, A., Garg, S., Singh, A.P., Bhatti, R., 2020. Protective effect of esculetin, natural coumarin in mice model of fibromyalgia: targeting pro-inflammatory cytokines and MAO-A. Neurochem. Res. 45, 2364–2374.
Sinha, S., Singh, K., Ved, A., Hasan, S.M., Mujeeb, S., 2022. Therapeutic journey and recent advances in the synthesis of coumarin derivatives. Mini Rev. Med. Chem. 22, 1314–1330.
Sloley, B., Urichuk, L., Morley, P., Durkin, J., Shan, J., Pang, P., Coutts, R., 2000. Identification of kaempferol as a monoamine oxidase inhibitor and potential neuroprotectant in extracts of *Ginkgo biloba* leaves. J. Pharm. Pharmacol. 52, 451–459.
Stafford, G.I., Pedersen, M.E., van Staden, J., Jäger, A.K., 2008. Review on plants with CNS-effects used in traditional South African medicine against mental diseases. J. Ethnopharmacol. 119, 513–537.
Stanton, R., To, Q.G., Khalesi, S., Williams, S.L., Alley, S.J., Thwaite, T.L., Fenning, A.S., Vandelanotte, C., 2020. Depression, anxiety and stress during COVID-19: associations with changes in physical activity, sleep, tobacco and alcohol use in Australian adults. Int. J. Environ. Res. Publ. Health 17, 4065.
Steru, L., Chermat, R., Thierry, B., Simon, P., 1985. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 85, 367–370.
Stringlis, I.A., De Jonge, R., Pieterse, C.M., 2019. The age of coumarins in plant–microbe interactions. Plant Cell Physiol. 60, 1405–1419.
Studer, L., Spenger, C., Seiler, R.W., Altar, C.A., Lindsay, R.M., Hyman, C., 1995. Comparison of the effects of the neurotrophins on the morphological structure of dopaminergic neurons in cultures of rat substantia nigra. Eur. J. Neurosci. 7, 223–233.
Sulakhiya, K., Keshavlal, G.P., Bezbaruah, B.B., Dwivedi, S., Gurjar, S.S., Munde, N., Jangra, A., Lahkar, M., Gogoi, R., 2016. Lipopolysaccharide induced anxiety-and depressive-like behaviour in mice are prevented by chronic pre-treatment of esculetin. Neurosci. Lett. 611, 106–111.
Tafet, G.E., Nemeroff, C.B., 2016. The links between stress and depression: psychoneuroendocrinological, genetic, and environmental interactions. J. Neuropsychiatry Clin. Neurosci. 28, 77–88.
Tan, R.X., Meng, J.C., Hostettmann, K., 2000. Phytochemical investigation of some traditional Chinese medicines and endophyte cultures. Pharmaceut. Biol. 38, 25–32.
Tremblay, A., Lingrand, L., Maillard, M., Feuz, B., Tompkins, T.A., 2021. The effects of psychobiotics on the microbiota-gut-brain axis in early-life stress and neuropsychiatric disorders. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 105, 110142.
Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Brizard, B., El Hage, W., Surget, A., Belzung, C., 2021. Neuroinflammation and depression: a review. Eur. J. Neurosci. 53, 151–171.
Trzepacz, P., van der Mast, R., 2002. The Neuropathophysiology of Delirium. Delirium in Old Age. Oxford University Press, Oxford, England.
Tsivileva, O.M., Koftin, O.V., Evseeva, N.V., 2022. Coumarins as fungal metabolites with potential medicinal properties. Antibiotics 11, 1156.
Udina, M., Navinés, R., Egmond, E., Oriolo, G., Langohr, K., Giménez, D., Valdés, M., Gómez-Gil, E., Grande, I., Gratacós, M., 2016. Glucocorticoid receptors, brain-derived neurotrophic factor, serotonin and dopamine neurotransmission are associated with interferon-induced depression. Int. J. Neuropsychopharmacol. 19, pyv135.
Van Eck, N., Waltman, L., 2010. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 84, 523–538.
Van Eck, N.J., Waltman, L., Dekker, R., Van Den Berg, J., 2010. A comparison of two techniques for bibliometric mapping: multidimensional scaling and VOS. J. Am. Soc. Inf. Sci. Technol. 61, 2405–2416.

Van Leeuwen, R., Swart, E., Boven, E., Boom, F., Schuitenmaker, M., Hugtenburg, J., 2011. Potential drug interactions in cancer therapy: a prevalence study using an advanced screening method. Ann. Oncol. 22, 2334–2341.

Vilar, S., Ferino, G., Quezada, E., Santana, L., Friedman, C., 2012. Predicting monoamine oxidase inhibitory activity through ligand-based models. Curr. Top. Med. Chem. 12, 2258–2274.

Wang, C., Lin, H., Yang, N., Wang, H., Zhao, Y., Li, P., Liu, J., Wang, F., 2019a. Effects of platycodins folium on depression in mice based on a UPLC-Q/TOF-MS serum assay and hippocampus metabolomics. Molecules 24, 1712.

Wang, D., Wang, X., Tong, W., Cui, Y., Li, X., Sun, H., 2019b. Umbelliferone alleviates lipopolysaccharide-induced inflammatory responses in acute lung injury by down-regulating TLR4/MyD88/NF-κB signaling. Inflammation 42, 440–448.

Wang, N., Wu, L., Cao, Y., Wang, Y., Zhang, Y., 2013. The protective activity of imperatorin in cultured neural cells exposed to hypoxia re-oxygenation injury via anti-apoptosis. Fitoterapia 90, 38–43.

Wang, R., Li, Y.-B., Li, Y.-H., Xu, Y., Wu, H.-l., Li, X.-J., 2008. Curcumin protects against glutamate excitotoxicity in rat cerebral cortical neurons by increasing brain-derived neurotrophic factor level and activating TrkB. Brain Res. 1210, 84–91.

Wang, X., Zhou, H., Wang, X., Lei, K., Wang, S., 2021. Design, synthesis, and *in vivo* and *in silico* evaluation of coumarin derivatives with potential antidepressant effects. Molecules 26, 5556.

Wei, Y., Xu, J., Miao, S., Wei, K., Peng, L., Wang, Y., Wei, X., 2022. Recent advances in the utilization of tea active ingredients to regulate sleep through neuroendocrine pathway, immune system and intestinal microbiota. Crit. Rev. Food Sci. Nutr. https://doi.org/10.1080/10408398.2022.2048291.

WHO, 2022. World Mental Health Report: Transforming Mental Health for All. World Health Organization, Geneva, 2022. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789240049338.

White-Gibson, A., O'Neill, B., Cooper, D., Michael Leonard, M., O'Daly, B., 2019. Levels of evidence in pelvic trauma: a bibliometric analysis of the top 50 cited papers. Irish J. Med. Sci. 188, 155–159. https://doi.org/10.1007/s11845-018-1818-x.

Winter, G., Hart, R.A., Charlesworth, R.P., Sharpley, C.F., 2018. Gut microbiome and depression: what we know and what we need to know. Rev. Neurosci. 29, 629–643.

Wu, L., Wang, X., Xu, W., Farzaneh, F., Xu, R., 2009. The structure and pharmacological functions of coumarins and their derivatives. Curr. Med. Chem. 16, 4236–4260.

Wu, M., Zhang, H., Zhou, C., Jia, H., Ma, Z., Zou, Z., 2015. Identification of the chemical constituents in aqueous extract of Zhi-Qiao and evaluation of its antidepressant effect. Molecules 20, 6925–6940.

Xie, Y., Huang, X., Hu, S.-y., Qiu, X.-j., Zhang, Y.-j., Ren, P., Wang, Y., Ji, H., Zhang, C.-h., Xie, W.-b., 2013. Meranzin hydrate exhibits anti-depressive and prokinetic-like effects through regulation of the shared alpha 2-adrenoceptor in the brain–gut axis of rats in the forced swimming test. Neuropharmacology 67, 318–325.

Xu, Q., Pan, Y., Yi, L.-T., Li, Y.-C., Mo, S.-F., Jiang, F.-X., Qiao, C.-F., Xu, H.-X., Lu, X.-B., Kong, L.-D., 2008. Antidepressant-like effects of psoralen isolated from the seeds of *Psoralea corylifolia* in the mouse forced swimming test. Biol. Pharm. Bull. 31, 1109–1114.

Yang, Y., Huang, H., Cui, Z., Chu, J., Du, G., 2021. UPLC–MS/MS and network pharmacology-based analysis of bioactive anti-depression compounds in betel nut. Drug Des. Dev. Ther. 4827–4836.

Yun, B.-S., Lee, I.-K., Ryoo, I.-J., Yoo, I.-D., 2001. Coumarins with monoamine oxidase inhibitory activity and antioxidative coumarino-lignans from *Hibiscus syriacus*. J. Nat. Prod. 64, 1238–1240.

Zhang, K., Yao, Y., Hashimoto, K., 2022. Ketamine and its metabolites: potential as novel treatments for depression. Neuropharmacology, 109305.

Zhou, W.-b., Zhang, X.-x., Cai, Y., Sun, W., Li, H., 2019. Osthole prevents tamoxifen-induced liver injury in mice. Acta Pharmacol. Sin. 40, 608–619.

Zhu, L., Nang, C., Luo, F., Pan, H., Zhang, K., Liu, J., Zhou, R., Gao, J., Chang, X., He, H., 2016. Esculetin attenuates lipopolysaccharide (LPS)-induced neuroinflammatory processes and depressive-like behavior in mice. Physiol. Behav. 163, 184–192.