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REVIEW

Anxiolytic, Antidepressant and Healthy Sleep-Promoting Potential of Rosmarinic Acid: Mechanisms and Molecular Targets

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Abstract: The etiology of psychiatric disorders is complex and results from intricate interactions among multiple neurobiological, psychological, environmental, and genetic factors. Furthermore, the roles of gut microbiome dyshomeostasis in their pathogeneses are just beginning to be uncovered, adding to another level of complexity. In recent years, significant efforts have been directed toward discovering multimodal yet safe therapeutics to counteract psychological deficits. Rosmarinic acid (RA), a polyphenol found in several medicinal herbs, has received considerable attention as a potential multifaceted therapeutic agent, particularly for neuropsychiatric conditions. In order to critically evaluate this aspect, data was compiled and consolidated after extensive searches on scholarly databases like PubMed, Google Scholar, and Web of Science. Peer-reviewed publications which focused on RA as a therapeutic agent for psychiatric disorders were included regardless of the year of publication and country of origin. Based on pre-clinical and clinical evidence, this review delves into the various mechanistic aspects of the antidepressant, anxiolytic, and sleep-promoting functions of RA. The beneficial effects of RA on the gut-microbiome-brain (GMB) axis and their implications for the regulation of neuroprotective pathways are also discussed, with a particular focus on exploiting them to ameliorate neuropsychiatric conditions. Our assessment indicated that RA is a multimodal neuroprotectant against psychiatric conditions and beneficially influences a plethora of targets related to redox, inflammatory, synaptic, cell death, neurotrophic, and cell signaling pathways. As a dietary agent, RA may also be relevant in favorably altering the GMB axis, indicating its prospects as a potential multimodal adjuvant therapeutic agent in regulating the pathogenic mechanisms underlying neuropsychiatric conditions. However, more extensive clinical studies are required to ascertain the neuromodulatory actions of RA in neuronal pathophysiologies, including psychiatric ailments.

Keywords: psychiatric disorders, circadian rhythm, gut-microbiome-brain axis, phytotherapy, traditional medicine

Introduction

Psychological conditions, such as stress, anxiety, and depression, have a tremendous impact on disability rates and overall quality of life. While the pathogenic mechanisms of these disorders rely on an intricately complex interaction between multiple neurobiological, genetic, and environmental factors, resident gut microbial species are also increasingly being perceived as a critical underlying element.[1] This emphasizes the necessity for thorough evaluations of multimodal treatment plans to address mental health disorders. Furthermore, the regimens should be safe with minimal or no adverse effects. In this regard, plant-based therapeutic agents isolated from traditional medicinal herbs are coming to the forefront.[2] Indeed, medicinal plants and their bioactive components have been shown to have promising therapeutic potential in neurological and psychiatric conditions.[3]

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Rosmarinic acid (RA) is a naturally occurring polyphenolic compound derived from hydroxycinnamic acid, which is found in many plants, predominantly in the *Lamiaceae* and *Boraginaceae* families.[4] It is a major bioactive compound found in medicinal herbs, such as rosemary (*Salvia rosmarinus*), lemon balm (*Melissa officinalis*), and spearmint (*Mentha spicata*), which are also used as dietary supplements.[5] RA extracted from these natural sources has been found to have immense potential applications for human health.[6] It offers a variety of medicinal uses, including anti-inflammatory, anti-cancer, antioxidant, anti-apoptotic, anti-aging, and neuroprotective applications.[7–9] With regard to central nervous system (CNS) disorders, RA supplementation is regarded as a potent multifaceted therapeutic intervention for ameliorating several pathological dysfunctions, lowering the risk of psychiatric conditions, and improving memory and cognition.[9,10] RA is also perceived as a promising therapeutic for sleep dysfunction,[11] which is often associated with psychiatric conditions, such as depression and anxiety.[12]

While the neuromodulatory and neuroprotective potential of RA is well known, only recently have research studies associated with RA supplementation shown beneficial alterations in the gut-microbiome-brain (GMB) axis. While previously published reviews on the neuroprotective activities of RA primarily cover its antioxidant, anti-inflammatory, and neurogenesis-promoting activities in neuropathologies in general,[9,10,13,14] the objective of the current review is to specifically delineate the underlying molecular and cellular mechanisms of RA-mediated antidepressant, anxiolytic, and healthy sleep-promoting actions. Furthermore, evidence for its utility, primarily as a prominent component of various plant-based extracts, in attenuating psychological dysfunction in humans is discussed in detail. Clinical evidences discussed in this review may bridge the gap between preclinical findings and their possible practical therapeutic applications. Indeed, such comprehensive and parallel assessment of the mechanisms and therapeutic potential of RA coupled with clinical insights may provide avenues for RA-based future clinical interventional approaches and for the development of personalized regimens for the treatment of psychological conditions. Additionally, RA's potential ability to positively modulate the GMB axis is currently under exploration, and the data suggests promising results, emphasizing its dietary relevance. Hence, based on recent reports, we implicate RA as a potent regulator of resident microflora, with a particular focus on the mental and psychological well-being of the host. Finally, we outline the limitations that have hindered the therapeutic use of RA to its full potential and suggest possible strategies to overcome these challenges.

Materials and Methods

The selection of pertinent primary research and review articles for compilation of this narrative review was performed using scholarly databases, such as PubMed (Medline), Google Scholar, and Web of Science. Multiple keyword combinations were employed for the literature search; {("rosmarinic acid") AND ("depression" OR "anxiolytic" OR "neuropsychiatric" OR "anxiety" OR "sleep" OR "gut microbiota" etc.)}. Few more search keywords such as "neuroprotection", "clinical trials", "gut-microbiome-brain", etc. were used. The retrieved articles were included in the study only after individualistic assessment of the titles and abstracts as well as a detailed inspection of the full texts. Furthermore, cited references in the retrieved articles and articles citing them were screened for pertinence and included if relevant. Articles were retrieved solely based on relevance, regardless of the publication timeframe. Articles in languages other than English were excluded, primarily because of the inability of the authors to comprehend other languages (and the ineffectiveness of language translation platforms in scholarly literature). The literature retrieved in this manner allowed for the collection of different articles presenting preclinical and clinical evidence for RA-mediated amelioration of psychiatric conditions.

RA and Mental Health

Several independent research groups have implicated RA as a potent anxiolytic, antidepressant, and normal sleep-promoting therapeutic.[9,15,16] It also elicits beneficial effects against psycho-behavioral anxiety- and depression-like comorbidities in neuropathologies, such as neuropathic pain,[17,18] epilepsy,[19,20] and Alzheimer's disease.[21,22] The underlying mechanisms of RA-mediated therapeutic actions for neuropsychiatric conditions of anxiety and depression appear to be multimodal and encompass the regulation of a plethora of endocrine, inflammatory, redox, and synaptic targets (Figure 1).

RA is the most relevant phytochemical constituent underlying the suppression of depression- and anxiety-like behavior of several traditional medicinal plants, such as *Perilla frutescens*,[23] *Micromeria myrtifolia*,[24] *Satureja montana*,[25] and *Origanum majorana*.[26] In this section, we focus on the anxiolytic and antidepressant actions of RA, detailing the cellular and molecular mechanisms underlying the inflammatory, oxidative, and synaptic regulation elicited by RA in neuropsychiatric conditions

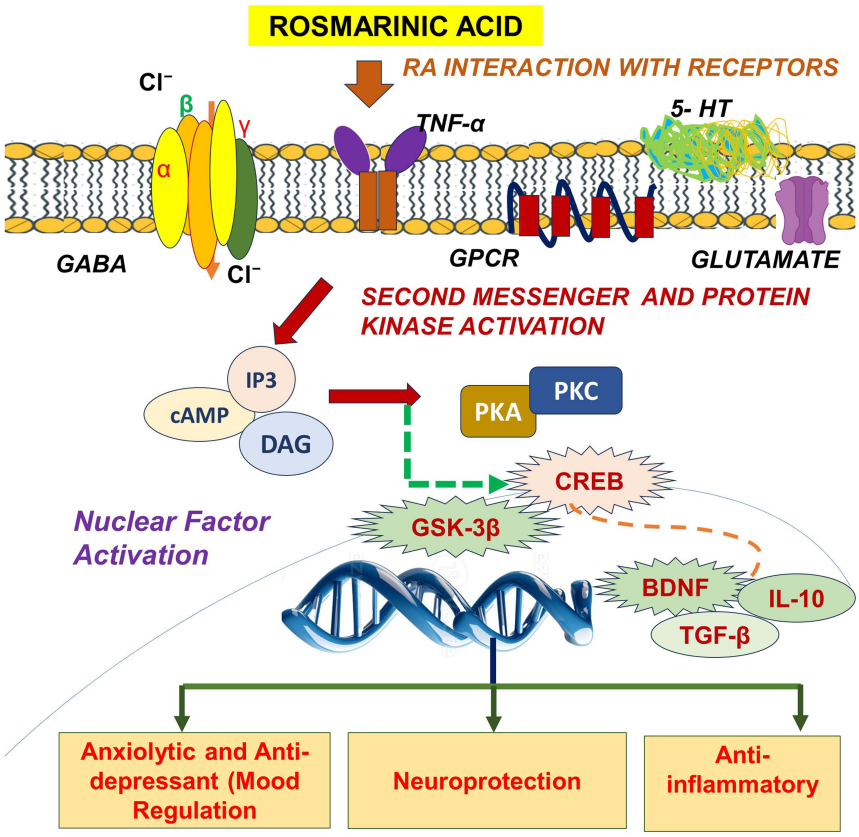

Figure 1 Molecular targets and mechanisms underlying the multimodal anxiolytic and antidepressant actions of RA. The figure illustrates the interactions of RA with different receptors, including TNF-α, 5-HT1, and GABA and glutamate receptors, resulting in beneficial modulation of second messenger intracellular pathways involving cAMP, IP3, and DAG. Downstream activation of cell signaling cascades involving protein kinases PKA, and PKC, as well as nuclear factors, CREB and GSK-3β mediate multifaceted neuroprotective effects. These include regulation of pro-inflammatory cytokine release, signaling thorough neurotrophic factors like BDNF, and anti-inflammatory mediators such as IL-10 and TGF-β, resulting in reduced inflammation, enhanced neuroprotection, and mood stabilization.
Abbreviations: TNF-α, tumor necrosis factor alpha; 5-HT1 receptor, 5-hydroxytryptamine (serotonin) receptor 1; GABA, gamma-aminobutyric acid; cAMP, cyclic adenosine monophosphate; IP3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PKA, protein kinase A; PKC, protein kinase C; CREB, cAMP response element-binding protein; GSK-3β, glycogen synthase kinase-3 beta; BDNF, brain-derived neurotrophic factor; IL-10, interleukin-10; TGF-β, transforming growth factor beta.

(Table 1). Implications of oral supplementation of RA as a therapeutic strategy against psychological and sleep disturbances in humans are discussed in a subsequent section. Furthermore, given the critical roles of the gut microbiome in the pathophysiology of the CNS,[27] we examined the implications of RA as an exogenous agent that regulates the GMB axis as a key facet of its therapeutic actions against neuropsychiatric ailments.

Table 1 Cellular and Molecular Mechanisms of RA-Mediated Anxiolytic and Antidepressant Actions

S. No.	Model	Intervention	Pathophysiological Actions	Molecular and Cellular Targets	Reference(s)
1	Male mice (25–28 g) subjected to chronic (14 days) restrain stress	Hydro-alcoholic extract of *Melissa officinalis* (containing 2.55, 3.825 and 7.65 mg/kg/day of RA; 14 days)	↓ depression- and anxiety-like behavior, ↓ oxidative damage, ↑ antioxidant capacity, ↑ anti-/pro-apoptotic markers	Lipid peroxidation, SOD, GPx, Bax, Bcl-2, cleaved caspase 3/pro-caspase 3	Ghazizadeh et al, 2020[28]
2	Male mice (6–8 weeks old) challenged with LPS	80 mg/kg RA	↓ depression- and anxiety-like, ↓ hippocampal neuronal damage, ↓ neuroinflammation, ↓ oxidative damage, ↑ antioxidant capacity, ↑ autophagy pathway, ↑ mitochondrial respiration	BDNF, p21, p62, NRF-2, LC3II, Beclin 1, CD44, iNOS, TNFα, and IL-1β, HO-1, NQO1, GCLC malic enzyme type 1 (ME1), isocitrate dehydrogenase 1 (IDH-1), 6-phosphogluconate dehydrogenase (6-PGDH)	Yu et al, 2022[29]

(*Continued*)

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Table 1 (Continued).

S. No.	Model	Intervention	Pathophysiological Actions	Molecular and Cellular Targets	Reference(s)
3	Rats subjected to chronic (40 days) unpredictable stress	RA at 25 and 50 mg/kg/day; 40 days	↓ depression-like behavior, ↓ corticosterone, ↑ serotonin, ↓ proinflammatory cytokines, ↓ oxidative stress and damage	Lipid peroxidation, glutathione, catalase, TNF-α, IL-6	Verma et al, 2022[30]
4	Rats subjected to chronic (21 days; between postnatal days 1 and 21) maternal separation stress	RA at 25 and 50 mg/kg/day; 21 days (between postnatal days 35 and 55)	↓ depression-like behavior, ↓ corticosterone, ↓ cell death, ↑ BDNF signaling, ↑ anti-inflammatory signaling, ↑ antioxidant capacity	Creatine kinase, LDH, BDNF, IL-10, glutathione, SOD	Verma et al, 2022[31]
5	Mice subjected to chronic restraint stress (2 hours/day; 14 days) and aged mice	30 mg/kg/day RA (30 min before daily restraint stress)	↓ MKP-1 signaling, ↑ BDNF signaling, ↑ CREB signaling, ↑ ERK-1/2 signaling, ↑ p38 signaling, ↑ JNK signaling	BDNF, p-CREB, PPARγ, SUV39H1, HDAC2, MKP-1, p-p38, p-JNK	Lee et al, 2019;[32] Lee et al 2021[33]
6	Male mice (3 weeks old) challenged with tail suspension-induced stress	5 and 10 mg/kg/day RA (7 days)	↓ corticosterone, ↓ MKP-1 signaling, ↑ catecholaminergic signaling	MKP-1, tyrosine hydroxylase, pyruvate carboxylase, BDNF, dopamine, noradrenaline, adrenaline	Kondo et al, 2015;[34] Sasaki et al, 2013[35]
7	Depression induced by corticosterone injection in 8 weeks old male mice	RA at 10 and 20 mg/kg/day; 21 days	↓ depression-like behavior, ↓ HPA axis activation, ↓ GR signaling, ↓ hippocampal neuronal damage, ↑ hippocampal neurogenesis	CRH, ACTH, corticosterone, GR, FKBP51, SGK1, HSP90, Synaptophysin and PSD95	Zeng et al, 2024[36]
8	Pentobarbital (40 mg/kg)-challenged mice	RA (2 mg/kg), and aqueous/ hydroalcoholic/ methanolic extract of *Salvia limbata*	↑ anxiolysis, ↑ sleeping time	GABA-A receptor subunit α1	Jahani et al, 2022[37]
9	Forced swim-induced depression in mice	RA (2 and 4 mg/kg) for 7 or 14 days	↓ depression-like behavior, ↑ hippocampal neurogenesis	ND*	Ito et al, 2008[38]
10	Newborn rats subjected to chronic (21 days) unpredictable stress	RA at 5 and 10 mg/kg/day; 14 days	↓ depression-like behavior	ERK1/2, BDNF	Jin et al, 2013[39]
11	Reserpine (4 mg/kg/day; 7 days)-induced depression in mice	50–400 mg/kg/day and 150–750 mg/kg/day of *Nepeta menthoides* (RA content: 11.2 ± 2.16 mg/g dried extract) and *Melissa officinalis* (RA content: 6.42 ± 1.10 mg/g dried extract) extract (7 days)	↓ depression-like behavior, ↑ antioxidant capacity	Catalase	Talebi et al, 2022[40]
12	Forced swim- and tail suspension-induced depression in male mice	25 mg/kg of RA	↓ despair behavior	MAO-A and B	Akkol et al, 2019[24]
13	Male mice (8 weeks and 2 months old) with spared nerve injury	1, 5 and 10 mg/kg/day of RA; 21 to 28 days post-surgery	↓ anxiety- and depression-like behavior, ↓ cellular senescence	β-galactosidase, IL-1β, IKB-α	Borgonetti and Galeotti, 2022;[17] Borgonetti and Galeotti, 2023[18]
14	Male rats (8 weeks old) subjected to acute cold (4 °C; 60 min) stress	250 and 500 mg/kg of *Satureja montana* (RA content: 44.7 ± 3.5 mg/g dried extract); and 15 mg/kg of RA	↓ anxiety- and depression-like behavior, ↑ social interaction	ND	Vilmosh et al, 2022[25]

(*Continued*)

Table 1 (Continued).

S. No.	Model	Intervention	Pathophysiological Actions	Molecular and Cellular Targets	Reference(s)
15	Epileptic 21–28 days old male mice (injected with 60 mg/kg pentylenetetrazol or 300 mg/kg pilocarpine)	3–30 mg/kg RA 30 min before pentylenetetrazol/ pilocarpine injection	↓ anxiety- and depression-like behavior	ND	Grigoletto et al, 2016[19]
16	Forced swim-induced psychological stress in rats	36 mg/kg/day RA (10 days)	↓ depressive phenotype, ↑ serotonergic signaling	5-HIAA, serotonin (5-HT)	Lin et al, 2015[41]
17	Maternally separated mice (3 hrs.; between postnatal days 2 to 14)	1, 2 and 4 mg/kg/day RA for 14 days (between postnatal days 40 to 54	↓ anxiety and repetitive/ obsessive phenotype, ↑ social interaction, ↓ neuroinflammation	TNF-α, IL-1β, iNOS, TLR4	Mahmoudian et al, 2024[42]
18	Male rats (2–3 months old)	2 or 8 mg/kg of RA	↑ anxiolysis, ↓ DNA damage	ND	Pereira et al, 2005[43]
19	Cecal ligation and puncture-induced sepsis in male mice (6–8 weeks old)	RA 20 mg/kg; 5 days before insult	↓ anxiety- and depression-like behavior, ↓ neuroinflammation, ↓ neuronal damage, ↑ synaptogenesis	IBA-1, iNOS, TNF-α, RACK1-HIF-1α	Liu et al, 2024[44]
20	Male rats injected with HIV tat protein, and subjected to chronic (restrain) stress (6 hr./day; 28 days)	10 mg/kg/day RA (14 days; from 14 days after start of chronic stress paradigm until the end of the paradigm)	↑ anxiolysis, ↓ corticosterone and HPA axis activation, ↑ BDNF	MR, GR, BDNF	Makhathini et al, 2018[45]
21	AD mice (hippocampal injection of $A\beta_{1\text{-}42}$)	100 mg/kg/day of *R. officinalis* extract, or 16 mg/kg/day RA (21 days post stereotaxic injection)	↑ anxiolysis, ↑ memory, ↓ neurodegeneration, ↑ neurogenesis, ↑ synaptogenesis	Ki67, NeuN, DCX, synaptophysin, synapsin, PSD-95	Mirza et al, 2021[22]
22	Male rats (8 weeks old) subjected to a an enhanced single prolonged stress protocol (constituting of sequence of stressful events such as restrain, forced swim, diethyl ether exposure and mild electric shock)	5 or 10 mg/kg/day of RA (14 days)	↓ anxiety-like behavior, ↑ hippocampal neurogenesis	ERK-1/2	Nie et al, 2014[46]

Abbreviations: SOD, superoxide dismutase; GPx, glutathione peroxidase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; p21, cyclin-dependent kinase inhibitor 1; p62, sequestosome-1; NRD-2, neurotrophin receptor-derived 2; LC3II, microtubule-associated protein 1A/1B-light chain 3-II; CD44, cluster of differentiation 44; iNOS, inducible nitric oxide synthase; TNFα, tumor necrosis factor alpha; IL-1β, interleukin-1 beta; HO-1, heme oxygenase-1; NQ01, NAD(P)H quinone dehydrogenase 1; IL-6, interleukin-6; IL-10, interleukin-10; LDH, lactate dehydrogenase; p-CREB, phosphorylated cAMP response element-binding protein; PPAR, peroxisome proliferator-activated receptor; SUV39H1, suppressor of variegation 3–9 homolog 1; HDAC2, histone deacetylase 2; MKP-1, mitogen-activated protein kinase phosphatase-1; p-JNK, phosphorylated c-Jun N-terminal kinase; p-38, phosphorylated p38 mitogen-activated protein kinase; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; GR, glucocorticoid receptor; FKBP51, FK506 binding protein 51; SGK1, serum/glucocorticoid regulated kinase 1; HSP90, heat shock protein 90; PSD95, postsynaptic density protein 95; ERK 1/2, extracellular signal-regulated kinases 1/2; MAO-A and B, monoamine oxidase A and B; IKB-α, inhibitor of nuclear factor kappa-B alpha; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin (5-hydroxytryptamine); TLR4, toll-like receptor 4; IBA-1, ionized calcium binding adapter molecule 1; RACK1-HIF-1α, receptor for activated C kinase 1-hypoxia inducible factor 1 alpha; MR, mineralocorticoid receptor; Ki67, antigen Ki67; NeuN, neuronal nuclei; DCX, doublecortin.

Redox Regulation

The brain is particularly sensitive to oxidative stress and neuronal injury, and redox dysregulation has been implicated as a primary mechanism of several neuropathologies, including neuropsychiatric ailments.[47] Amelioration of dysregulated redox pathways is a critical facet of the potent anxiolytic and antidepressant functions of RA. Thus, RA was shown to ameliorate behavioral deficits in open field, elevated plus maze, tail suspension and forced swim paradigms in mice challenged with restraint stress, in part by rescuing dysfunction of the neuronal antioxidant pathways, particularly those centered on superoxide dismutase (SOD) and glutathione peroxidase (GPx) enzymes.[28] An Iranian research group identified RA as the major bioactive accounting for the antidepressant action of medicinal herbs, *Nepeta menthoides* and *Melissa officinalis*.[40] Further experimental analyses indicated that the antidepressant potential of these RA-containing herbal extracts was due to the ability of RA to stimulate brain catalase activity. Verma et al recently showed that RA rescues depression-like behavior in chronic unpredictable stress (CUS)-exposed,[30] and in chronic maternal separation-

challenged rats, probably via mitigation of deficits in the antioxidant, inflammatory, and serotonergic pathways. The authors proposed restoration of the defects in corticosterone, brain-derived neurotrophic factor (BDNF), creatine kinase, oxidative (glutathione and SOD), inflammatory (interleukin 10; IL-10), and cell death pathways as the major mechanisms underlying RA-mediated antidepressant effects.[31] These results indicate that the antioxidant system of SOD is a primary target of RA-mediated antidepressant actions in CUS, in agreement with those obtained by Gavzan et al.[48] Depressive comorbidity linked to lipopolysaccharide (LPS)-induced hippocampal neuroinflammation has been shown to be repressed by RA via activation of nuclear factor erythroid 2-related factor 2 (NRF-2) signaling, resulting in significant induction of antioxidant enzymes, heme oxygenase 1 (HO-1), NAD(P)H-quinone oxidoreductase (NQO1), and glutamate–cysteine ligase catalytic subunit (GCLC).[29]

Interestingly, gender appears to be a significant mediator of the therapeutic actions of RA, including neuroprotection. For instance, supplementation of RA has been shown to elicit sex-dependent modulation of hippocampal functions, including oxidative, immune-related and sex hormone signaling.[49] While RA supplementation is associated with memory improvements in both aged male and female rodents, it leads to altered lipid metabolism in young adults. The underlying mechanisms of these alterations appear to be gender-specific; in males, glycemic signaling is impaired, while in females, BDNF signaling may be the more prominent target.[50] Hence, it is plausible that peripheral metabolic and endocrinological parameters influence RA's actions. Indeed, previous literature suggests that RA, along with other polyphenols, is involved in regulating sex hormone pathways. Thus, a study done on screening natural compounds and potential drugs against breast cancer indicated that RA binds strongly to the active site and inhibits aromatase, an enzyme responsible for estrogen biosynthesis, supporting its potential in regulating sex hormone pathways.[51] Along similar lines, Zych et al[52] have suggested that RA can modulate certain metabolic and oxidative parameters under conditions of estrogen deprivation, such as those experienced by ovariectomized rats. These findings indicate that RA, in addition to its antioxidant effects, could modulate hormone levels and control metabolic parameters, possibly in a gender-specific manner. However, further studies are warranted to clearly establish gender as a moderator of the actions of RA on pathophysiological processes, particularly those related to emotionality and psychological functions.

Neuroinflammation

Dyshomeostasis of neuroinflammatory signaling is another relevant therapeutic target for psychological conditions such as depression and anxiety. Given the potent anti-inflammatory actions of RA,[53] it is hardly surprising that studies have implicated neuroinflammatory pathways as potential underlying mediators of RA's beneficial effects. Hence, RA was found to prevent depressive and anxiety-like behavior in rodents subjected to the cecal ligation and puncture (CLP) paradigm of sepsis.[44] In the CLP-induced sepsis in male mice, RA had shown to prevent neuronal damage and induce synaptogenesis, likely due to normalization of neuroinflammatory responses, including attenuation of microglial M1 polarization, as assessed by the levels of ionized calcium-binding adapter molecule 1 (IBA-1), inducible nitric oxide synthase (iNOS), and tumor necrosis factor alpha (TNF-α). The authors further implicated the receptor for activated C kinase/hypoxia-inducible factor 1 alpha (RACK/HIF-1α) signaling as a key target of RA-mediated antidepressant and anxiolytic actions in sepsis. In a recently published study, RA was found to attenuate the effects of maternal separation-induced psychological stress in mice by prompting appreciable reductions in the levels of pro-inflammatory mediators, TNF-α, IL-1β, toll-like receptor 4 (TLR4), and iNOS.[42] Mitigation of neuroinflammatory responses as a module of antidepressant activities of RA has also been proposed by Yu et al, who showed that RA markedly reduced the expression of pro-inflammatory mediators, iNOS, CD44, TNF-α, and IL-1β, by rescuing the deficits in BDNF/Nrf2 signaling.[29]

Synaptic Signaling

Monoaminergic signaling has been known as a therapeutic target for RA-mediated antidepressant and anxiolytic actions. Indeed, pharmacological assessments in animal models of stress and depression have established serotonergic, noradrenergic and dopaminergic systems as chief underlying players.[54] Lin et al have also implicated serotonin and signaling through its postsynaptic receptors as mediators of antidepressant actions of RA.[41] Kondo et al evaluated the underlying mechanisms of RA's antidepressant in rodents challenged with tail suspension stress, and found that it causes significant

upregulation of tyrosine hydroxylase (TH) and pyruvate carboxylase, enzymes which are known regulators of dopaminergic, serotoninergic and GABAergic signaling.[34,35] Further, stimulated hippocampal catecholaminergic signaling in their study was found to be associated with repressed mitogen-activated protein kinase phosphatase-1 (MKP-1) signaling, as well as with enhanced BDNF signaling.[34] Cell culture experiments using RA in corticosterone-challenged PC12 cells confirmed its cytoprotective actions and positive influences on dopaminergic, serotonergic, and GABAergic pathways. Increased production of the neurotransmitters dopamine, serotonin, norepinephrine, and acetylcholine was proposed to be dependent on the cell kinase systems of mitogen-activated protein kinase (MAPK) and ERK-1/2.[35]

While previous studies have suggested that the antidepressant activities of RA may not depend on monoamine oxidase (MAO) or synaptic uptake of monoaminergic neurotransmitters,[55] recent studies indicate that RA can influence the monoaminergic system by altering the expression and activation status of monoamine oxidase isoforms A (MAO-A)[56] and B (MAO-B).[57] Indeed, IC_{50} of RA for MAO-A and MAO-B have been found to be 6.5 and 5.3 mg/mL.[24] Acetylcholinesterase (AChE) hydrolyzes acetylcholine in the synaptic cleft, and thereby influences signaling at the cholinergic synapses. AChE appears to be a key synaptic target for the RA-mediated antidepressant and anxiolytic actions. Cellular models have confirmed the ability of RA to significantly alter AChE activity.[58] In fact, direct high-affinity binding of RA to AChE has been confirmed using in silico analyses.[59]

GABAergic signaling is another target of RA in the psychological conditions of anxiety and depression. For instance, Ibarra et al found that RA, as a principal bioactive in *Melissa officinalis* extract, repressed anxiety-like behavior of rodents in open field and elevated plus maze tasks by repressing GABA transaminase, elevating brain GABA levels.[60] These findings are in concurrence with a recent study, wherein the authors proposed that the anxiolytic efficacy of RA-containing *Melissa officinalis* extract is due to its ability to inhibit GABA transaminase and MAO-A enzymes, and stimulate the cellular endogenous antioxidant potentials.[61] Further, anxiolytic and hypnotic actions of Persian medicinal herb *Salvia limbata* in pentobarbital-challenged mice have been proclaimed to be dependent principally on RA as the major constituent; pharmacological assessment indicated the involvement of α1 subunit-containing GABA-A receptors in RA-mediated anxiolysis and sedation.[37] Similarly, RA was found to potentiate hypnotic and anxiolytic actions of pentobarbital by stimulating the expressions of GABA producing enzyme, glutamic acid decarboxylase (GAD) and GABA-A receptor subunits, α3, α4, α5, β2 and γ3.[62] Recently, based upon ex vivo synaptosomal and in silico experiments, a direct binding and activation of GABA-A receptors has been proposed for RA.[63] Interestingly, Kim et al have also proposed involvement of adenosine receptors, A_1-R and A_{2A}-R, in normal sleep-promoting functions of RA, which probably also involved altered neuronal activity of cholinergic and GABAergic signaling in two key sleep-regulating brain regions, lateral hypothalamus and ventrolateral preoptic nucleus, respectively.[64]

Anti-Apoptotic Signaling

RA, a significant bioactive compound in *Melissa officinalis* hydroalcoholic extract, has been shown to restore anti-apoptotic/pro-apoptotic balance in the prefrontal cortical and hippocampal brain regions of mice challenged with chronic restraint stress.[28] Specifically, the authors found that repression of depression-like behavior, as assessed by elevated plus maze, forced swimming, and tail suspension paradigms, was associated with increased expression of anti-apoptotic marker, Bcl-2; as well as depressed levels of pro-apoptotic markers Bax and cleaved caspase 3/pro-caspase 3 ratio. In addition to relieving hyperalgesia in neuropathic pain, RA mitigated comorbid symptoms of anxiety, depression, and sleep disturbances in mice. RA-induced neuroprotective effects in a spared nerve injury (SNI) model were possibly due to suppression of neuroinflammatory responses, which in turn caused attenuation of cellular senescence, as assessed by the diminished levels of marker protein, β-galactosidase.[17,18] Furthermore, Shahrestani et al have also proposed apoptotic mediator, caspase 3 as a critical mediator of neuroprotective and anxiolytic functions of RA.[65] Mitigation of genotoxic brain DNA damage as assayed by the comet assay in rats may be another mechanism underlying RA-mediated anxiolysis.[43] More recently, results from pentylenetetrazole (PTZ)- and pilocarpine-challenged mice indicate that sleep promoting activities of RA may stem from its ability to limit redox alterations and prevent DNA damage in the hippocampal and cortical brain regions.[20]

Neurotrophic and Neurogenic Pathways

Neurotrophic signaling involving BDNF and its TrkB receptor has been implicated as a major factor in the regulation of RA-mediated anxiolytic and antidepressant functions. Therefore, Kondo et al reported robust antidepressant effect of RA when administered orally at doses 5 and 10 mg/kg for 7 consecutive days in depressive male mice, likely via stimulatory actions on BDNF signaling.[34] Probably, the best example of involvement of BDNF signaling in mediating the beneficial actions of RA in depressive states comes from animal studies, which show that RA can efficiently reduce depressive symptoms associated with brain ageing. For example, RA supplementation in aged mice with weak psychological stress-induced depression appears to result in appreciable antidepressant actions.[33] These have been shown to alleviate stress-induced alterations in the SUV39H1 histone methyltransferase-related epigenetic pathways controlling the expression of BDNF and mitogen-activated protein kinase phosphatase-1 (MKP-1). Furthermore, RA-mediated mitigation of depression-like psycho-behavioral abnormalities in mice subjected to chronic restraint stress may also be dependent on its ability to alter epigenetic players, such as histone deacetylase 2 (HDAC2) and SUV39H1, in a CREB and peroxisome proliferator-activated receptor-gamma (PPARγ) signaling-dependent manner.[32] Subsequently, the activation of HDAC2 and SUV39H1 caused by RA ultimately weakened MKP-1 signaling, concomitantly with stimulation of the extracellular signal-regulated kinase 1/2 (ERK1/2), p38, and c-Jun N-terminal kinase (JNK) cascades. Anxiogenic effects associated with exposure to HIV protein tat and repetitive restrain stress were observed to be significantly attenuated by RA, possibly via normalization of HPA axis signaling, and stimulation of BDNF signaling.[45] Similarly, the ability of RA to normalize BDNF signaling in rodent models of depression associated with LPS-induced neuroinflammation has been implicated in attenuation of neuronal damage, normalization of hyperactivated inflammatory responses, activation of NRF-2 antioxidant signaling, stimulation of mitochondrial bioenergetic functions, and correction of autophagic imbalances.[29] Hippocampal BDNF and ERK1/2 signaling cascades have also been evidenced to the chief targets of RA-mediated repression of depressive behavior in CUS-exposed Sprague-Dawley rats.[39]

In a chemically induced rodent model of AD, RA was shown to harbor anxiolytic and memory-enhancing activities, possibly because of its ability to stimulate hippocampal neurogenic and synaptogenic pathways, as assessed by the expressions of marker of proliferation Kiel 67 (Ki67), neuronal nuclear protein (NeuN) and doublecortin (DCX); and synaptophysin, postsynaptic density protein-95 (PSD-95), and synapsin I–III, respectively.[22] Similarly, the antidepressant actions of RA in a rodent model of forced swim-induced depression were proposed to be reliant on hippocampal dentate gyrus neurogenesis, as assessed by significant increases in BrdU-positive cells.[38] More recently, stimulation of BNDF/TrkB/CREB- and PI3K/Akt/mTOR-mediated hippocampal neurogenesis and synaptogenesis has been implicated as critical aspect of RA-induced antidepressant actions.[36] This study also identified glucocorticoid receptor (GR) signaling, glucocorticoid-inducible kinase 1 (SGK1), heat shock protein 90 (HSP90), and FK506-binding protein 51 (FKBP51) as key targets of RA in preventing neuronal loss in corticosterone-challenged mice. Lataliza et al have additionally implicated PPARγ and cannabinoid receptors CB-1/2 receptor signaling as a target of RA-mediated antidepressant functions in a chemically induced rodent model of neuroinflammation.[66] Lastly, using a combinatorial paradigm of multiple sequential stressful events (physical restraint, forced swimming, loss of consciousness induced by exposure to anesthetic diethyl ether, and mild electric foot shock), Nie et al confirmed the potent anxiolytic actions of RA in rats.[46] Further, they found that RA robustly stimulated hippocampal neurogenesis in an ERK-1/2 signaling cascade-dependent manner.

RA and Human Psychiatric Health: Evidences from Clinical Studies

RA, either alone or as the major bioactive component of herbal extracts, has been tested for its anxiolytic, antidepressant, and sleep-promoting potential in several studies (Table 2). Lemon balm, which is enriched in RA, is the most widely used plant source for the formulation of oral herbal extracts in human studies. Indeed, a meta-analysis of multiple trials conducted in diverse groups of human subjects has confirmed that supplementation of its extract is associated with robust improvements in depression and anxiety scores.[67] Further, dried leaf extract from lemon balm has been shown to improve mood and cognition attributes of young healthy adults.[68,69] An extract formulated from lemon balm dried leaves, both as an aqueous beverage and as an added ingredient in yogurt-based drink, has been evidenced to uplift mood and have

Table 2 Summary of Recent Studies Evaluating the Antidepressant, Anxiolytic and Hypnotic Activities of RA-Containing Herbal Formulations in Human Clinical Trials

S. No.	Model	Intervention	Pathophysiological Actions	Molecular and Cellular Targets	Reference(s)
1	20–25 years old university students (34 placebo; 34 supplemented)	*Rosmarinus officinalis* extract at the dose of 500 mg twice a day, for 4 weeks	HADS, PSQI, and PRMQ	↓ anxiety and depression, ↓ sleep impairment, ↑ memory functions	Nematolahi et al, 2018[77]
2	18–55 years old newly diagnosed MDD subjects (25 placebo; 26 supplemented)	*Rosmarinus officinalis* extract (21.13 ± 0.56 mg RA/g dry extract) at the dose of 350 mg twice a day, for 8 weeks	HADS-A, and BDI-II	↓ anxiety and depression	Azizi et al, 2022[78]
3	18–65 years old healthy adults with mild emotional distress and sleep dysregulation (48 placebo; 52 supplemented) NR	*Melissa officinalis* Relissa™ extract (400 mg/day) for 3 weeks	DASS-42 and, PSQI	↓ anxiety and depression, ↑ normal sleep functions, ↑ emotional well-being	Bano et al, 2023[71]
4	20–65 years old male and female subjects with diabetic mellitus type 2 (21 placebo; 23 supplemented) 20–65 years	*Melissa officinalis* extract (700 mg/day) for 12 weeks	BDI-II, BAI, and PSQI	↓ anxiety and depression, no changes in sleep quality	Safari et al, 2023[72]
5	Male and female sleep dysregulated subjects above 18 years of age (27 placebo; 31 supplemented)	*Melissa officinalis* leaf extract (400 mg) as one of the component of a formulation dissolved in 200 mL of warm water for 6 weeks	PSQI, and actigraphy data (Fitbit Charge 5)	No changes in sleep quality	Gutiérrez-Romero et al, 2024[74]
6	Alzheimer's disease subjects (age > 59 years) with mild dementia (10 placebo; 10 supplemented)	*Melissa officinalis* extract (containing 500 mg RA) for 24 weeks	NPI-Q, MMSE, ADAS-cog, DAD, and CDR	↑ neuropsychiatric score, no improvement in cognition and AD-related biomarkers, no adverse effects on safety parameters	Noguchi-Shinohara et al, 2020[75]
7	18–23 years old healthy young adults (undergraduates) (n = 20, used as placebo controls and treatment group at intervals of 7 days)	*Melissa officinalis* extract (600, 1000 or 1600 mg)	Bond–Lader Visual Analog Scales, and CDR computerized assessment	↑ calmness, ↑ quality and speed of memory	Kennedy et al, 2003[68]
8	40–75 years old patients with chronic stable angina (38 placebo; 35 supplemented)	*Melissa officinalis* extract (3 g/day) for 8 weeks	DASS-21, and PSQI	↓ depression, anxiety and stress, ↓ sleep disturbances	Haybar et al, 2018[73]

(*Continued*)

Table 2 (Continued).

S. No.	Model	Intervention	Pathophysiological Actions	Molecular and Cellular Targets	Reference(s)
9	23–28 years old healthy young adults (n = 25, used as placebo controls and treatment group at different times)	*Melissa officinalis* extract (0.6 g containing >6% RA) in ice tea-like beverage or yoghurt, 3 hr. before testing	STAI, DASS, MTF, POMS, CDR core battery, and VAS	↓ anxiety, ↓ salivary cortisol levels, ↑ cognitive functions	Scholey et al, 2014[70]
10	50–70 years old subjects with age-associated memory impairment (29 placebo; 28 and 30 supplemented with 600 or 900 mg/day of extract)	*Mentha spicata* extract (600 or 900 mg/day) for 90 days	POMS, LSEQ, and CDR system	↓ mood disturbances, ↑ sleep quality, ↑ memory functions	Herrlinger et al, 2018[79]
11	Young (18–35 years) and older (36–50 years) healthy subjects (54 placebo; 52 supplemented)	*Mentha spicata* extract (900 mg/day) for 90 days	POMS, LSEQ, PSQI, and computerized cognitive assessment (CNS Vital Signs Inc).	no changes in mood and sleep attributes, ↑ attention	Falcone et al, 2019[80]
12	22–50 years old subjects with mild sleep impairments (46 placebo; 43 supplemented)	485 mg/day of "Polyphenol botanical blend (PBB)" containing at least 65 mg RA for 30 days	PSS, CESD, POMS, ISI, PSQI, and actigraphy data (Fitbit Charge 5)	No effects on stress and depression levels, ↑ sleep quality, ↑ neurocognitive abilities (attention, risk assessment and working memory)	Tubbs et al, 2021[81]

Abbreviations: HADS, Hospital Anxiety and Depression Scale, PSQI, Pittsburgh Sleep Quality Index, PRMQ, Prospective and Retrospective Memory Questionnaire, HADS-A, Hospital Anxiety and Depression Scale-Anxiety Subscale, BDI-II, Beck Depression Inventory-2nd Edition, DASS-42, Depression, Anxiety, and Stress Scale with 42 items, BAI, Beck Anxiety Inventory, NPI-Q, Neuropsychiatric Inventory Questionnaire, MMSE, Mini-Mental State Examination, ADAS-cog, Alzheimer's Assessment Scale-Cognitive Subscale, CDR, Cognitive Drug Research, DAD, Disability Assessment for Dementia scale, CDR, Clinical Dementia Rating, STAI, State-Trait Anxiety Inventory, DASS, Depression, Anxiety, and Stress Scale, MTF, Purple Multi-Tasking Framework, POMS, Profile of Mood States, CDR core battery, Cognitive Drug Research core battery, VAS, Bond-Lader Visual Analogue Scales, PSS, Perceived Stress Scale, CESD, Center for Epidemiological Studies Depression Scale, ISI, Insomnia Severity Index.

anxiolytic and cognition-enhancing effects in healthy young adults.[70] Supplementation of RA-rich lemon balm leaf extract in emotionally distressed subjects with sleep dysregulation was also found to result in significantly improved psychological, emotional and sleep functions.[71] Similar results of elevated mood and sleep attributes in diabetic patients orally supplemented with lemon balm hydroalcoholic extract have been reported by Safari et al.[72] Lemon balm extract has also been evaluated for its beneficial effects on psychological and sleep attributes in patients suffering from chronic angina.[73] Questionnaire (depression anxiety stress scale; DASS-21 and Pittsburgh sleep quality index; PQSI)-based results indicated robust declines in the depression, anxiety, stress and sleep disturbance scores in subjects supplemented with lemon balm formulation, over the placebo-controls. More recently, lemon balm, as part of a combinatorial nutraceutical formulation, has been tested for its beneficial effects on neuropsychological parameters in Colombian subjects with sleep impairments. Interestingly, no beneficial effects on sleep parameters were observed in subjects supplemented with the formulation when compared to the placebo-controls.[74] It is possible that complementation of lemon balm with other ingredients of the nutraceutical concoction results in the loss of sleep-promoting properties. In a recent study of subjects diagnosed with Alzheimer's disease and mild dementia, Noguchi-Shinohara et al observed improvements in neuropsychiatric scores upon oral supplementation with RA-enriched lemon balm extract; however, no effects on performance in cognitive tests were observed.[75] In a subsequent study, the same authors showed that supplementation of the extract prevented cognitive decline in aged adults without hypertension.[76]

Other medicinal plant extracts rich in RA have also been tested in human trials. For instance, supplementation of spearmint extract in aged subjects with memory impairments has been observed to result in attenuation of mood and sleep disturbances, in addition to the beneficial effects on working and spatial memory domains of cognition.[79] On the other hand, this extract did not alter the mood, sleep and cognitive (except the attention module) attributes of normal healthy young adults and middle-aged subjects, over the placebo-controls,[80] indicating that the extract may not result in any additional changes in subjects with normal sleep and psychological functions . Interestingly, Dabagzadeh et al used RA-containing rosemary extract in university students and provided evidence for its potent beneficial actions on psychological (depressive and anxious behavior), sleep, and cognitive parameters.[77] Subsequently, they extended their findings of anti-anxiety, antidepressant, and cognition-stimulating potencies of rosemary extract in subjects diagnosed with major depressive disorder (MDD).[78] Lastly, an herbal formulation comprising RA, among other polyphenols, was shown to attenuate sub-clinical sleep disturbances and promote healthy sleep patterns.[81]

RA, GMB Axis and Psychiatric Health

The resident microbial population is instrumental for the intricate network of communication between the gut and the brain, controlling multiple aspects of CNS functions.[27,82] Recent research has confirmed tremendous involvement of the GMB axis in controlling the pathophysiology of psychiatric conditions,[83,84] as well as sleep disorders.[85,86] Indeed, dysbiosis of the resident microbial populations, and hence alterations in the levels of metabolites derived from them, may predispose individuals to mental health abnormalities such as depression, schizophrenia, and autism spectrum disorder.[87] On the other hand, psychological stress-induced variations in HPA axis activity may affect microbial composition.[88] Genetic factors add another level of complexity to this bidirectional interaction connecting the GMB axis and the pathogeneses of psychological conditions.[89] Recent research has uncovered the involvement of a plethora of cellular mechanisms linked to neurotransmitter, endocrine, metabolic, redox and immune signaling in these intricate connections. Given the multifaceted interactions between the GMB and etiology of psychological conditions, it is not surprising that the GMB axis is increasingly being regarded as a critical therapeutic target for mental health conditions of depression and anxiety.[90,91] In this regard, medicinal plants-derived polyphenols, such as RA, have the potential to serve as safe and effective ameliorative agents.[92,93] Interestingly, gut microflora may produce catabolic enzymes capable of converting polyphenols such as RA to more active, better-absorbed metabolites, further increasing their therapeutic potential as antidepressants.[94] Indeed, gut microbe-mediated metabolism of RA into metabolites such as caffeic acid may also direct enhanced production of short chain fatty acids (SCFAs), regulating pathways of host inflammation and oxidative stress, and eventually enhancing its therapeutic efficiency.[95] Several recent reports support the hypothesis that RA influences the GMB in neuropsychiatric conditions (Figure 2). The key aspects of these findings are discussed below.

RA-rich *Rosmarinus officinalis* extract mitigates depressive phenotype in a mouse model of chronic restrain stress-induced behavioral changes, as assessed by time spent in the central region of open field maze, and immobility time in tail suspension and forced swim tests.[96] Upon metabolomic analyses, it was found that the *Rosmarinus officinalis* extract significantly enhanced proportions of the species of the *Lactobacillus* and *Firmicutes* phyla, while reducing the *Bacteroidetes* and *Proteobacteria* content in the gut of the treated stressed mice. The changes in the resident intestinal microflora induced by RA-containing herbal concoction were associated with attenuation of the activities of neuroinflammatory mediators, IL-1β, TNF-α, NF-κB, p65 and IBA-1, as well as activation of neurogenic (BDNF) and cell survival (Akt) pathways in hippocampi.[96] Ou et al observed significant attenuation of dysbiosis of the resident microflora upon supplementing diabetic rats with RA at a dose of 30 mg/kg for 8 weeks.[97] Specifically, RA increased the quantities of bacterial species from the *Actinobacteria, Proteobacteria, Verrucomicrobia* and *Fusobacteria* phyla. Prominent bacteria whose intestinal levels were upregulated and restored by RA are *Anaerostipes, Coprococcus* and *Sutterella*, all of which have been shown to be negatively associated with depressive phenotypes in humans.[98,99] On the other hand, RA repressed the elevated levels of unfavorable bacteria, *Desulfovibrio* and *Flavonifractor*, which are positively associated with depression.[100,101] Similarly, a two-week *Melissa officinalis* extract (containing 2.76 ± 0.05 mg RA/100 mg of dried extract) oral supplementation paradigm in obese mice abolished dysbiosis of gut microflora, specifically resulting in increased expression of *Porphyromonadaceae* species.[102] Of note, intestinal numbers of *Porphyromonadaceae* have been previously shown to be reduced in association with depressive/anxious behavior

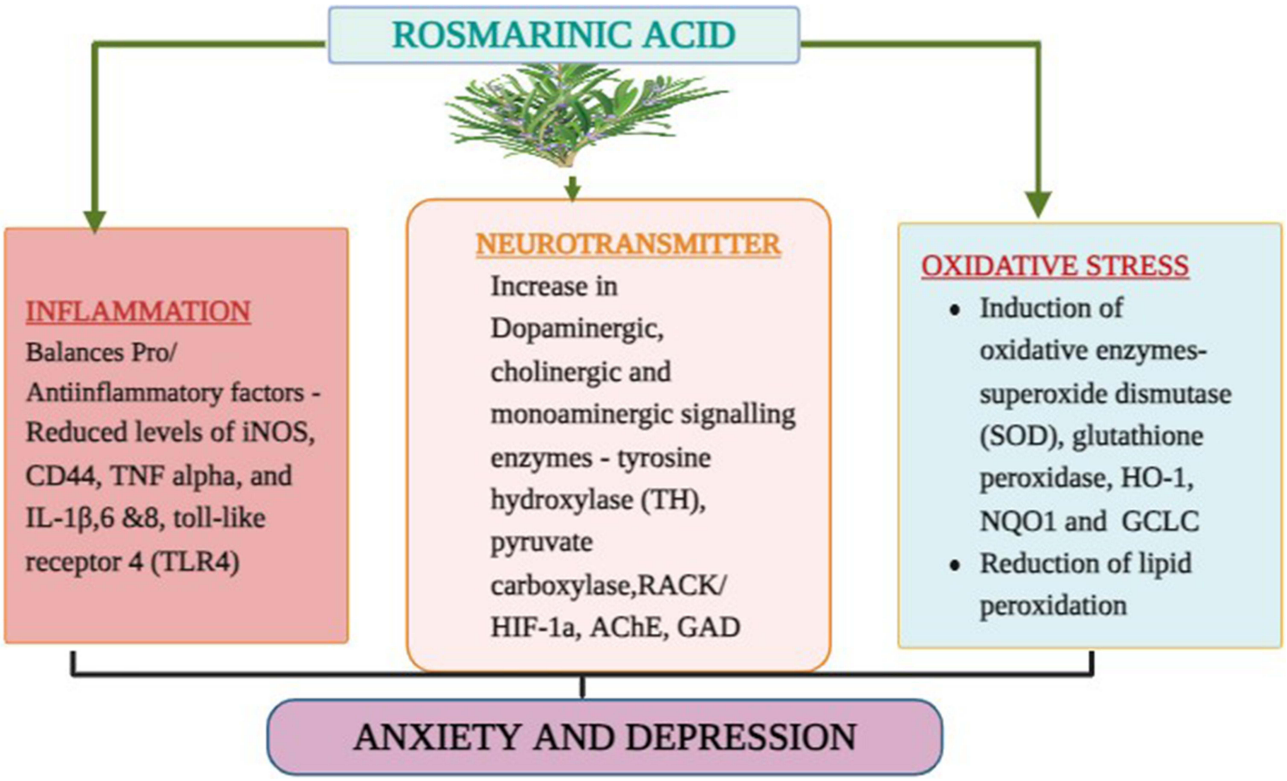

Figure 2 RA as a therapeutic agent to ameliorate gut microflora dysbiosis. A number of pathways including redox, inflammatory, metabolic and cell survival are targets of RA-gut microbiota interactions.
Abbreviations: PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SCFA, short-chain fatty acids; SOD, superoxide dismutase.

induced by "emotional-single prolonged stress",[103] and elevated in response to treatment with antidepressants.[104] Another study conducted in high-fat diet-induced obese mice confirmed the therapeutic actions of RA, as a principal component of *Thymus serpyllum* extract, in mitigating oxidative and inflammatory damage and promoting metabolic and cell survival pathways.[105] These physiological alterations occurred concomitantly with significant restoration of resident microbial ecological diversity (as measured by the *Bacteroidetes*/ *Firmicutes* ratio) and upregulation of SCFA-producing bacteria. Furthermore, intestinal abundances of *Faecalibaculum, Mucispirillum* and *Rikenella* were reduced upon supplementation with *Thymus serpyllum* extract in these obese mice. Notably, *Faecalibaculum* spp. have been shown to induce depressive behavior in mice.[106] Similarly, *Mucispirillum*[107] and *Rikenella*[108] are thought to positively regulate the development of depressive behavior.

Chemically induced rodent models of colitis have been particularly useful for studying the effects of RA-enriched natural medicinal formulations on the intestinal microflora. For instance, oral supplementation of monofloral honey from *Prunella vulgaris*, containing RA as the major phenolic compound, was observed to restore gut microbial homeostasis in favor of *Firmicutes*/*Bacteroidetes* ratio, particularly increasing the abundances of *Lactobacillus* bacteria in colitic rats.[109] Similarly, rape bee pollen extract has been shown to increase the abundances of *Lactobacillus, Prevotella* and *Akkermansia* and *Adlercreutzia* species, and reduce the amounts of *Paraprevotella* and *Allobaculum* in the gastrointestinal tract of colitic mice.[110] While probiotic bacteria of *Lactobacillus*[111] and *Adlercreutzia*[112] genera are known to repress depression-like behavior, high relative abundances of *Paraprevotella* are thought to show positive associations with neuropsychological dysfunctions.[113] Similarly, *Akkermansia*, one of the bacterial species favorably affected by RA-containing rape bee pollen-derived extract supplementation, may positively regulate certain pathophysiology aspects of psychological disorders.[114] Further, *Prevotella* elicits relatively lowered expression in depressive individual, compared to healthy controls. Likewise, fecal expression of *Allobaculum* is probably associated with attenuation of the depressive phenotype.[115]

The favorable effects of RA-containing honey on resident microbial populations are supported by results from studies that have assessed the supplementation of RA-enriched plant-based extracts as a therapeutic strategy against colitis. Indeed, the traditional Chinese herbal concoction *Mosla chinensis* Maxim. cv. Jiangxiangru (JXR), which harbors RA as the major bioactive, was shown to stimulate the expression of gut bacteria belonging to the *Bifidobacteriales* and *Melainabacteria* phyla, while repressing the amounts of *Bacteroidaceae* species.[116] Interestingly, a recent study has proposed that reductions in copy numbers of gut *Melainabacteria* may contribute to the development of depression-like phenotype.[107] Zhou et al successfully used RA-containing *Thymus vulgaris* extract to reduce colitic and inflammatory damage to dextran sulfate sodium (DSS)-challenged mice and reported enhanced proportions of SCFA-producing bacteria belonging to the *Blautia, Bacteroides, Romboutsia*, and *Faecalibaculum* phyla.[117] On the other hand, the extract repressed gut expression of harmful microflora, *Escherichia, Shigella* and *Muribaculum*, which are implicated as pro-inflammatory mediators in the pathophysiology of depression.[118,119] Repression of host pro-inflammatory signaling, via enhanced intestinal abundances of *Lactobacillus* and reduced amounts of *Romboutsia*, has also been suggested as the therapeutic basis for the anti-colitis effects of RA-containing *Dracocephalum moldavica* extract in rodents.[120] Notably, intestinal expression of *Romboutsia* is thought to be positively associated with resilience to depression and anxiety.[121,122]

RA-encapsulated nanoformulations (corresponding to daily administration of 1 and 10 mg/kg RA for 4 days) have been shown to repress the intestinal copy numbers of *Firmicutes, Bacteroidetes, Clostridium leptum*, and *Bacteroides* in rats, resulting in increased fecal levels of SCFAs, such as butyrate and reduced levels of poly-unsaturated fatty acids (PUFAs), including omega-3 and 6 fatty acids.[123] Interestingly, PUFAs are positively associated with the pathogeneses of depressive symptoms;[124] while bacterial production of SCFA butyrate may be antidepressive.[125] As part of its remedial actions on oxidative, inflammatory and apoptotic injuries, RA as the major bioactive in the ethanolic extract derived from the leaves of *Trichodesma khasianum*, has also been shown to attenuate ethanol-induced dysbiosis of the resident microflora and stimulate the gut microbial production of SCFA by increasing the amounts of *Muribaculaceae* and *Ruminococcaceae* bacteria in mice.[126] Results from a subsequent study from the same lab further provided evidence for the involvement of gut microbial species in the ameliorative effects of *Trichodesma khasianum* extract in high-fat diet fed obese mice, wherein it stimulated *Bacteroidetes*/*Firmicutes* proportions, specifically resulting in increased copy numbers of *Lactobacillus, Muribaculaceae* and *Ruminococcaceae* bacteria.[127] Interestingly, *Ruminococcaceae* family of bacteria has been previously shown to be significantly repressed in the intestines of depressive individuals.[128]

In contrast to the gut microbial-modifying actions of phyto-concoctions, RA alone has been shown to significantly and beneficially alter gut microflora. Hence, in a mouse model of ovalbumin-induced intestinal allergy, supplementation with RA was shown to repress pro-inflammatory signaling, in part by beneficially altering the *Firmicutes*/*Bacteroidetes* ratio, specifically changing the abundance of *Muribaculaceae, Lactobacillus* and *Prevotella*,[129] all of which have been implicated in the pathogenesis of depression.[113,130] RA as an individual therapeutic has also been evaluated for its effectiveness in ameliorating DSS-induced inflammatory and colitic injuries in mouse intestinal tissues. The results indicated significant mediation of the gastrointestinal microflora on the remedial actions of RA, involving an increased abundance of probiotics of the *Bacteroidaceae, Alistipes* and *Muribaculaceae* phyla. Furthermore, RA supplementation was associated with significant upregulation of gut microflora-mediated SCFA production.[131] Of note, *Alistipes* and *Muribaculaceae* species have been implicated as possible regulators of host butyrate-producing capacity in the patho-physiology of depression.[130,132] Finally, Li et al proposed that the anti-inflammatory, antioxidant, and anti-apoptotic actions of RA in a murine model of inflammatory bowel disease (IBD) may rely on its ability to favorably alter gut microbiota. Specifically, they showed that oral RA supplementation reduced the intestinal amounts of *Bifidobacterium pseudolongum, Escherichia coli*, and *Romboutsia ilealis* and increased the quantity of *Lactobacillus johnsonii*.[133] Interestingly, studies indicate that *Lactobacillus johnsonii* may be associated with improvements in depressive symptoms.[134]

In conclusion, recent studies suggest that RA, both alone and as a prominent component of natural medicinal preparations, ameliorates resident gut microbial dyshomeostasis and reverses pathophysiological changes in multiple disease states (Figure 3). The mechanisms underlying the therapeutic connections between RA supplementation and microflora involve the regulation of inflammatory, metabolic, oxidative, and cell survival signaling cascades. These pathways form the basis for the therapeutic potential of RA in depression and anxiety. Hence, although few studies have

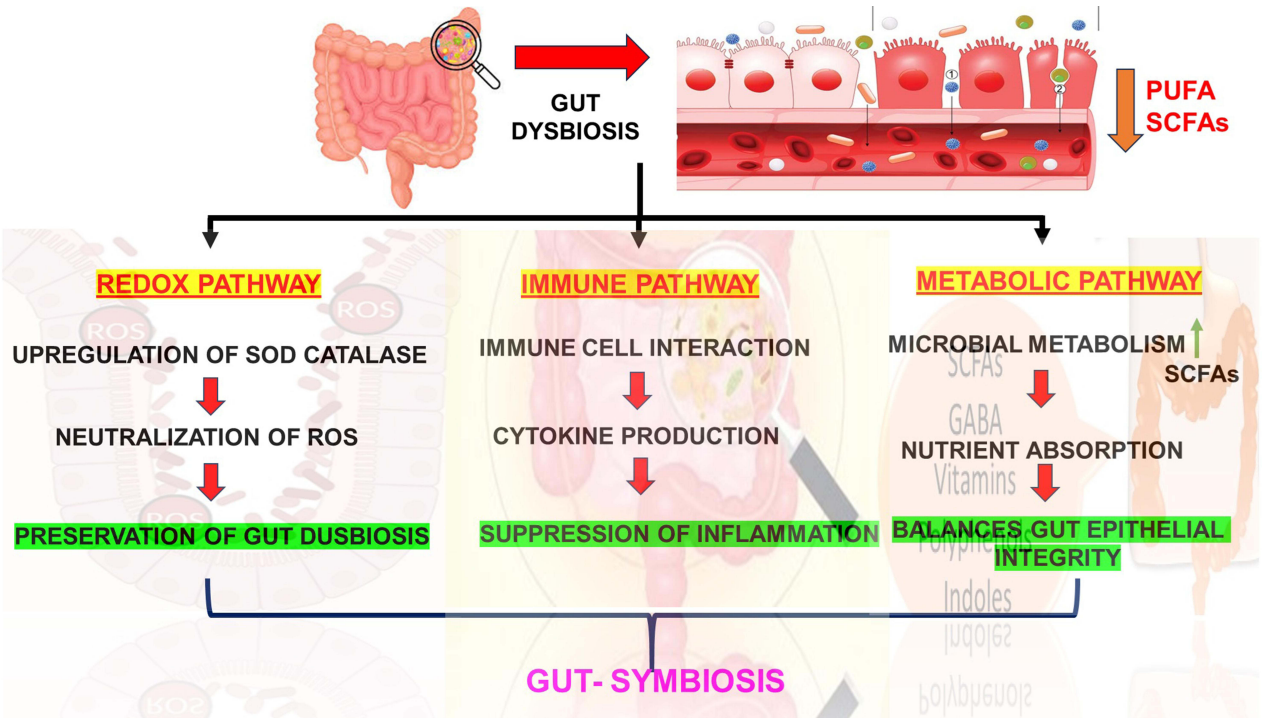

Figure 3 Proposed mechanisms linking therapeutic actions of RA and gut microbial dysbiosis in psychological disorders. RA-mediated beneficial effects on the host–microbe interactions in psychological conditions may involve regulation of inter-connected target pathways of redox, immune, endocrine and synaptic signaling.
Abbreviations: PUFAs, polyunsaturated fatty acids; SCFAs, short-chain fatty acids.

explicitly evaluated the relevance of the intestinal microbiota in RA-mediated antidepressant and anxiolytic functions, it is likely that host-bacterial interactions form a key aspect of RA-based therapeutic regimens. However, this needs to be experimentally tested in future pre-clinical and clinical studies.

Discussion

Two important aspects must be conidered in order to fully establish RA a therapeutic agent; its safety and its bioavailability. RA and plant-based extracts containing RA have been widely recognized for safe administration at physiologically relevant doses. Studies pointed out the negligible toxicity effects of RA-containing plant extracts in rats and mice.[135,136] Further, one of the significant studies has reported no toxicity effect upon administration of 500 mg of RA extract from lemon balm (*Melissa officinalis*) in healthy human subjects. The results from hematological assessment were favorable, indicating no adverse effects on blood and liver as well as kidney functions.[137] Similar findings have been reported upon oral administration of lemon balm extract in patients with mild cognitive impairment[76] and human subjects suffering with Alzheimer's disease.[75] In concurrence, a placebo-controlled randomized clinical study using RA extract of aqueous spearmint on human subjects with aging-associated memory impairments found no significant changes in different biochemical and hematological toxicity parameters.[138] Studies have also confirmed the insignificant deleterious effects of different nanoformulations loaded with RA on multiple parameters indicative of gut microbiome dysbiosis, liver and kidney dysfunction, and hematological, biochemical, genotoxic and cytotoxic, and oxidative damage.[123,139] In contrast, minor levels of toxic effects on reproductive and organ functioning, as well as genetic integrity, have been reported for exceedingly high and chronic doses of RA-containing extracts.[140] This indicates that the necessity of an in-depth research on the safety and drug interaction aspects of high doses of rosemary and other RA-rich plant extracts.

Given their potent therapeutic potential, several studies have been conducted to identify ways to increase the yield of RA. Novel biotechnological modifications have resulted in high RA yield from hairy root cultures, suspension cultures, undifferentiated cell cultures, and plant metabolic engineering production.[5] In this regard, it should be noted that

pharmacokinetics and metabolism of RA following its oral ingestion has been described somewhat in greater detail,[9,141] compared to most phytochemicals. The majority of absorbed RA is gradually eliminated in the urine after oral consumption.[142] In addition, RA may be excreted in the form of its sulfate-conjugated derivatives in urine, as observed in rodents.[143] The low bioavailability of orally supplemented RA is a major obstacle,[144] however, multiple groups have proposed measures to increase the bioavailability. These include the creation of RA-phospholipid complexes,[145] chitosan-based polymer conjugates,[146,147] esterification using alkyl chains of varying lengths,[148] and co-employment of piperidine to prevent RA glucuronidation.[149] More recently, hydrophobic ion pair (HIP) complexes and HIP-loaded lipid nanocapsules have been proposed as effective nanofabrication methods to address the low bioavailability of RA.[150] Moreover, solid lipid nanoformulations of RA have been shown not to induce damages associated with renotoxicity, hepatotoxicity, hematotoxicity, genotoxicity, cytotoxicity, and oxidative and metabolic stress.[123] With regard to CNS disorders, nanotechnological procedures may represent a suitable strategy for enhancing the brain bioavailability of RA, particularly through the nasal route (reviewed by Fachel et al).[151] Nevertheless, further studies are warranted to improve the permeability and absorption of orally supplemented RA and enhance its sustained and efficient delivery to maximally exploit RA's therapeutic potential in neuropsychiatric conditions.

Conclusion

In conclusion, this review tracks the multifaceted effects of RA associated with psychological disorders with a focus on the GMB axis, supported by evidence from clinical and non-clinical data. To convert these discoveries into practical applications, additional extensive research is necessary to optimize the doses of RA in different medical conditions, address long-term safety concerns, and discern the precise mechanisms of action. Further research is required to determine and regulate the long-term effects of RA on the gut microbiota and brain inflammation to clarify and evaluate the safety and efficacy of RA at different doses. Furthermore, specific biological and neurological mechanisms underlying the beneficial actions of RA on gut microbiota, brain functions, and mental health, in association with other antidepressant treatments and dietary practices, and their potential synergistic effect, should also be discovered to draw appropriate therapeutic possibilities. We hope that the present review will serve as a relevant research platform for further investigation into these undiscerned aspects of the influence of RA on the pathophysiology of psychological disorders.

Abbreviations

AChE, acetylcholinesterase; BDNF, brain-derived neurotrophic factor; CB-1/2, cannabinoid receptors 1/2; CNS, central nervous system; CUS, chronic unpredictable stress; DASS-21, depression anxiety stress scale; DCX, doublecortin; DSS, dextran sulfate sodium; ERK1/2, extracellular signal-regulated kinase 1/2; FKBP51, FK506-binding protein 51; GAD, glutamic acid decarboxylase; GCLC, glutamate–cysteine ligase catalytic subunit; GMB, gut-microbiome-brain; GPx, glutathione peroxidase; GR, glucocorticoid receptor; HDAC2, histone deacetylase 2; HIP, hydrophobic ion pair; HO-1, heme oxygenase 1; HSP90, heat shock protein 90; IBA-1, ionized calcium-binding adapter molecule 1; IBD, inflammatory bowel disease; IL-10, interleukin 10; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; Ki67, Kiel 67; LPS, lipopolysaccharide; MAO, monoamine oxidase; MAO-A, monoamine oxidase isoform A; MAO-B, monoamine oxidase isoform B; MDD, major depressive disorder; MKP-1, mitogen-activated protein kinase phosphatase-1; NeuN, neuronal nuclear protein; NQO1, NAD(P)H-quinone oxidoreductase; NRF-2, nuclear factor erythroid 2-related factor 2; PPARγ, peroxisome proliferator-activated receptor-gamma; PQSI, Pittsburgh sleep quality index; PSD-95, postsynaptic density protein-95; PTZ, pentylenetetrazole; PUFA, poly-unsaturated fatty acid; RA, rosmarinic acid; RACK/HIF-1α, receptor for activated C kinase/hypoxia-inducible factor 1 alfa; SCFA, short-chain fatty acid; SGK1, glucocorticoid-inducible kinase 1; SOD, superoxide dismutase; TH, tyrosine hydroxylase; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alfa.

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Disclosure

The authors report no conflicts of interest in this work.

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