

Biomedical features and therapeutic potential of rosmarinic acid

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Abstract For decades, the use of secondary metabolites of various herbs has been an attractive strategy in combating human diseases. Rosmarinic acid (RA) is a bioactive phenolic compound commonly found in plants of *Lamiaceae* and *Boraginaceae* families. RA is biosynthesized using amino acids tyrosine and phenylalanine via enzyme-catalyzed reactions. However, the chemical synthesis of RA involves an esterification reaction between caffeic acid and 3,4-dihydroxy phenyl lactic acid contributing two phenolic rings to the structure of RA. Several studies have ascertained multiple therapeutic benefits of RA in various diseases, including cancer, diabetes, inflammatory disorders, neurodegenerative disorders, and liver diseases. Many previous scientific papers indicate that RA can be used as an antiplasmodic, anti-viral and anti-bacterial drug. In addition, due to its high anti-oxidant capacity, this natural polyphenol has recently gained attention for its possible application as a nutraceutical compound in the food industry. Here we

provide state-of-the-art, flexible therapeutic potential and biomedical features of RA, its implications and multiple uses. Along with various valuable applications in safeguarding human health, this review further summarizes the therapeutic advantages of RA in various human diseases, including cancer, diabetes, neurodegenerative diseases. Furthermore, the challenges associated with the clinical applicability of RA have also been discussed.

Keywords Rosmarinic acid · Bioactive phenolic compounds · Natural products · Drug discovery · Anti-cancer therapy

Introduction

The phenolic compound rosmarinic acid (RA) is commonly produced by *Boraginaceae* and subfamily *Nepetoideae* of the *Lamiaceae* plant species. The presence of RA is confined to the *Lamiaceae* family and in others, including monocotyledonous, dicotyledonous, and hornworts and ferns (Petersen et al. 2009). Originally RA, an attractive phytochemical, was extracted as a pure compound from rosemary (*Rosmarinus officinalis*), an evergreen perennial aromatic herb. In addition to RA, rosemary produces a variety of other secondary metabolites, including terpenes, essential oils, and flavonoids. Structurally, RA is an ester of caffeic acid and 3,4-dihydroxy phenyllactic acid originating from aromatic amino acids, phenylalanine, and tyrosine, respectively (Dewick 2002). Biosynthesis of RA from amino acid precursors phenylalanine and tyrosine involve eight enzymatic reactions and is deduced from studies conducted on cell suspensions of *Coleus blumei* (Razzaque and Ellis 1977). However, the increasing demand for RA has spurred efforts for the biotechnological production of RA through

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cell cultures that provide higher yields (Khojasteh et al. 2020; Li et al. 2019). RA and its derivatives such as lithospermic acid, rabdossin, and salviaionic acid exhibit potent biological actions combating various human diseases such as cancer, diabetes, apoptosis, neurodegenerative disorders, cardiovascular disease, and inflammatory disorders (Kim et al. 2015, 2017, 2020c; Jeong and Hwang 2021; Jin et al. 2021b; Lee et al. 2021; Koprivica et al. 2022). RA prevents ultraviolet rays-induced photodamage (Gupta et al. 2021; Huerta-Madroñal et al. 2021). Pattananandecha et al. (2021) reported anti-oxidant activity and anti-photoaging effects of RA extracts on UVA-mediated damage on human fibroblast from the *Thunbergia laurifolia* plant. Figure 1 demonstrates RA's anti-inflammatory, anti-oxidant, anti-microbial, anti-diabetic, anti-cancer, and anti-hypertensive potential (Bulgakov et al. 2012; Zhang et al. 2021a).

In addition, several studies have reported that the dietary supplementation of herbs (rosemary, ginkgo, chamomile, and garlic) containing bioactive components (RA, quercetin, and thymol) improve immune responses, anti-oxidant status, and also lowered morbidity and mortality rates in animals and poultry (Alagawany and Abd El-Hack 2015). Bioinformatics and network-based analysis have demonstrated that RA could act on several target genes involved in inflammatory responses, anti-oxidant balance, tumor initiation, and progression to form a systemic pharmacological network (Guan et al. 2021). RA has been extensively studied for its therapeutic roles and nutraceutical properties to improve human and animal health based on its remarkable pharmacological and medicinal characteristics (Choi

et al. 2016; Değer and Çavuş 2020; Kim et al. 2021b). In recent years, the design and development of potential nutraceutical and efficacious medicinal products from natural sources have attracted considerable interest (Alam et al. 2021, 2022). However, the effectiveness of such bioactive compounds depends on intake, their stability, and bioavailability. Here we attempt to summarize the recent updates on biological applications of RA and critically review its therapeutic potential and health benefits. This review also provides deeper mechanistic insights into the therapeutic effectiveness of RA in combating common metabolic diseases. We further provide a comprehensive understanding of RA's pharmacokinetic profile and updated clinical status as a potential drug molecule.

Structural features of RA

RA and related compounds were considered tannins of the *Labiata* plants earlier. They were later discovered as a pure compound from *Rosmarinus officinalis* by two Italian chemists in 1958. The chemical structure of RA ($C_{18}H_{16}O_8$) is derived from hydroxycinnamic acid and has a chiral center with R and S enantiomers formed by rotation. RA appears as a crystalline solid with a molar mass of 360.2 g/mol and a melting point of 171–175 °C. RA is a highly lipophilic compound with a slight hydrophilic nature and therefore exhibits maximum solubility in organic solvents. The density of RA was assessed to be 1.54 g/cm³ and dissociation constant (pKa) of 3.57.

Biosynthesis of RA

Identified first in *Coleus blumei*, the biosynthesis of RA is a complex and non-linear enzyme-catalyzed process that begins with aromatic amino acids phenylalanine and tyrosine (Petersen and Simmonds 2003). Phenylalanine is deaminated to cinnamic acid by phenylalanine ammonia-lyase (PAL) enzyme of lignin through flavonoid biosynthetic pathway. Subsequently, the benzene ring of cinnamic acid is hydroxylated by cytochrome-P450 monooxygenase cinnamate-4 hydroxylase of flavonoid pathway forming 4-coumaric acid (Petersen 1997). Later hydroxycinnamic acid is activated by hydroxycinnamate: coenzyme A ligase (Petersen and Simmonds 2003). On the other hand, 4-hydroxyphenyllactic acid is derived from the precursor tyrosine by transamination to 4-hydroxy phenyl pyruvic acid. The transformation is catalyzed by tyrosine aminotransferase. 4-hydroxyphenylpyruvic acid is further reduced to 4-hydroxyphenyllactic acid by hydroxyphenylpyruvate reductase requiring NADH and NADPH as co-substrates (Trócsányi et al. 2020).

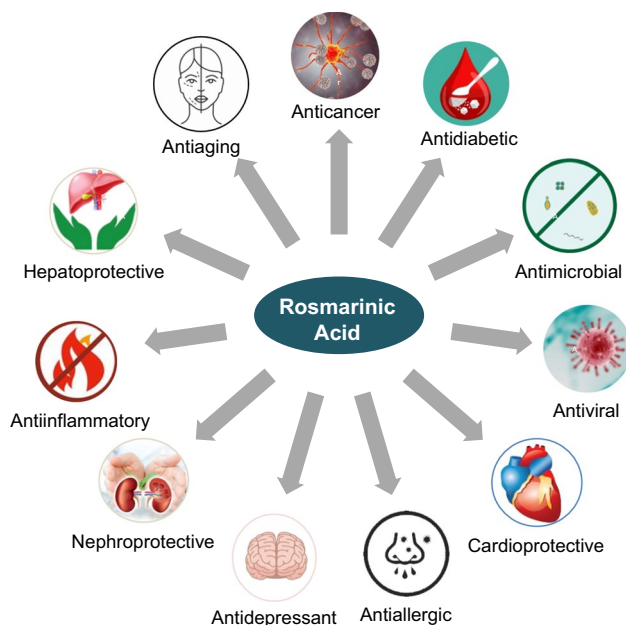


Fig. 1 Pharmacological effects of RA on human health

In the next biosynthetic step, 4-coumaroyl CoA is derived by phenylalanine transformation and 4-hydroxyphenyllactate from tyrosine combined with tyrosine 4-coumaroyl-4'-hydroxyphenyllactic acid to release coenzyme A. The ester linkage between the carboxyl group of 4-coumaric acid and the hydroxyl group of 4-hydroxyphenyllactate is formed by hydroxycinnamoyl-CoA: hydroxyphenyllactate-hydroxycinnamoyl transferase, also known as rosmarinic acid synthase (Petersen et al. 1993). Lastly, 4-coumaroyl-4-hydroxy phenyllactate is hydroxylated at 3 and 3' position on aromatic rings by cytochrome P450 monooxygenases.

Pharmacological properties of RA

A multitude of biological roles of RA and similar compounds have been documented in earlier scientific literature (Marchev et al. 2021). These reports describe RA as an anti-inflammatory, anti-oxidant, and anti-microbial compound (Swarup et al. 2007). Since ancient times, RA has been used in folk medicine, cosmetics, and dietary supplements. The health-promoting benefits of RA could be based on scavenging reactive oxidation species, decreasing nitric oxide production, lipid peroxidation, increasing high-density lipoprotein, decreasing low-density lipoprotein levels, and deranged hemolysis (Baba et al. 2004; Guo et al. 2020). Nyandwi et al. (2021b) has reported lipid-lowering effects of RA through modulation of reverse cholesterol transport-related proteins, thereby combating hyperlipidemia-based disorders. RA also increased macrophage cholesterol influx via regulation of ABCA1 transporter expression through JAK2/STAT3, JNK, and PKC-p38 and ABCA2 expression JAK2/STAT3, JNK, and PKC-ERK1/2/p38 (Nyandwi et al. 2021a). Earlier scientific literature has also reported the role of RA in modulating several enzymes involved in the progression of several diseases, including diabetes, cancer, and inflammatory disease (Nadeem et al. 2019). Few studies elucidating RA-mediated enzyme inhibition have been listed in Table 1. The most interesting therapeutic role and mechanism of action of RA are detailed in the following subsections.

Anti-inflammatory potential

Inflammation is a vital component of innate immunity that initiates protective responses and healing cascades. The inflammatory process maintains immune system homeostasis and significantly impacts human health (Yi et al. 2017). The rapid recruitment of granulocytes marks acute inflammation, whereas macrophages and cytokine release by T cells are involved in chronic inflammation. The sustained inflammatory stage promotes chronic inflammation causing life-long debilitating illnesses such as irritable bowel

syndrome, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis (Luo et al. 2020a). Most immunosuppressants or steroidal therapy treatments often prove inadequate and impose potent side effects. Bioactive components from natural herbs such as essential oils, flavonoids, phenols promote anti-inflammatory responses. As mentioned previously, RA exerts profound anti-inflammatory effects, and many in vivo and in vitro studies have reported the anti-inflammatory potential of RA in inflammatory diseases (Gonçalves et al. 2022).

T cell subset involved in the development and progression of rheumatoid arthritis is an important therapeutic target. RA induced T-cell apoptosis via cytochrome leakage blocks mitochondrial membrane potential disruption, and a reduced Bcl-2 production was observed in RA patients (Hur et al. 2007). RA application has been reported to influence collagen biosynthesis in a few studies (Sutkowska et al. 2021). Youn et al. (2003) found improved arthritic index and many affected hind paws in murine models of collagen-induced arthritis. In addition, prolonged treatment by RA significantly ameliorated collagen-induced arthritis judged by reduced synovitis and depleted COX-2 expressing cells in affected joints. Similarly, RA purified from Mexican mint was found to inhibit RANKL-induced osteoclastogenesis via downregulation of the NF- κ B signaling pathway in cell culture (Phromnoi et al. 2021). Interestingly, RA enhanced osteo-integration of osteoblast cells on titanium surface by improving osteoblast cell differentiation, mineralization, and bone formation via the RANKL/RANK/OPG pathway (Jeong et al. 2021).

Moreover, RA significantly diminished IL-1 β and TNF- α release ameliorating collagen-induced arthritis under in vivo conditions (Hsu et al. 2011). Hu et al. (2018) showed the protective effect of RA on rat chondrocytes by inhibiting extracellular matrix degradation in osteoarthritis. RA antagonized catabolic activity of IL-1 β inhibited matrix-degrading enzymes and inflammatory molecules. Recently, RA isolated from *Punica granatum* showed anti-arthritic potential in Freund's complete adjuvant-induced arthritic rat model. The study concluded the implication of RA in clinical settings for the therapeutic management of arthritis (Gautam et al. 2019). The above findings suggest RA as a potential novel therapy for inflammatory joint disorders.

The incidence of chronic intestinal inflammation has increased worldwide, especially in developing countries. Current treatment modalities lack a complete cure for intestinal inflammatory diseases. Consequently, the need for effective and safe natural compounds becomes attractive in treating inflammatory bowel diseases. RA and other natural compounds have been extensively studied for clinical implications in intestinal inflammation (Formiga et al. 2020). Studies have reported ameliorative effects of RA on dextran sulfate-induced ulcerative colitis in mice models. RA markedly suppressed colonic inflammation via dual inhibition

Table 1 Enzyme Inhibition Constant Data of RA from Binding DB

S. No	Target	Disease	IC50 (nM)	Assay description	Reference
1	HIV type 1 integrase	Acquired immuno-deficiency syndrome	4000	Inhibition of strand transfer activity of HIV-1 integrase	Mazumder et al. (1997)
2	Tyrosine-protein kinase Lck	Cancer, autoimmune disorders, chronic inflammatory diseases	24,000	Inhibition of binding to p56 Lck tyrosine kinase SH2 domain	Park et al. (2003)
3	Matrix metalloproteinase-2	Cancer, arthritis, skin aging, blood vessel impairment	27,200	Inhibition of gelatinolytic activity of MMP2 in rat lung homogenate after 40 min by SDS-PAGE preincubated for 30 min	Murata et al. (2009)
4	Aldose reductase	Diabetes	3910	Inhibition of aldose reductase	Koukoulitsa et al. (2010)
5	Tyrosinase	Skin melanization	250,000	Inhibition of mushroom tyrosinase	Fujimoto et al. (2010)
6	Transcription factor AP-1	Rheumatoid arthritis and cancer	16,200	Inhibition of transcription factor AP-1 binding to oligonucleotide containing TPA-responsive element in TPA-activated human HeLa cells after 1 h	Chen et al. (2014)
7	Interstitial collagenase	Rheumatoid arthritis, fibrotic disease	5600	Inhibition of human recombinant MMP1 catalytic domain using Dnp-Pro-beta-cyclohexyl-Ala-Gly-Cys(Me)-His-Lys-(Nma)-NH ₂ as substrate pre-incubated	Yuan et al. (2013)
8	Proto-oncogene tyrosine-protein kinase Src	Cancer	26,000	Inhibition of c-SRC SH2 domain	Sperl et al. (2009)
9	Estradiol 17-beta-dehydrogenase 2	Osteoporosis	3720	Inhibition of human 17beta-HSD2 expressed in HEK293 cell lysates incubated for 10 min using [2,4,6,7-3H]-estradiol and NAD+ by scintillation	Vuorinen et al. (2017)
10	Beta amyloid A4 protein	Alzheimer's disease	71,900	Inhibition of amyloid beta (1 to 42 residues) (unknown origin) aggregation after 24 h by thioflavin T assay	Kwon et al. (2015)
11	Reverse transcriptase	Acquired immuno-deficiency syndrome	100,000	Inhibition of HIV1 reverse transcriptase	Dubois et al. (2008)
12	Integrase	Acquired immuno-deficiency syndrome	63,500	Inhibition of HIV1 integrase using labelled oligonucleotide substrate in presence of bovine serum albumin by ELISA	Dubois et al. (2008)
13	Aldose reductase	Diabetes complications	3890	Inhibition of <i>Rattus norvegicus</i> (rat) lens aldose reductase	Jain et al. (2012)
14	Tyrosine-protein kinase Fyn	Neurodegenerative disease	1300	Inhibition of human Fyn expressed in Sf9 cells after 20 min by ELISA in presence of 1 umol/L ATP	Jelić et al. (2007)
15	Lipoxygenase	Cancer, asthma, inflammatory disease	1,150,000	Inhibition of soybean lipoxygenase in vitro. Binding energy and IC-50 calculated to detect inhibitory activity	Koukoulitsa et al. (2007)
16	MARK-4	Cancer	6200	Inhibition of MARK-4 validated in cell-free and cell-based enzyme assay. Increased apoptosis in MARK-4 overexpressing cancer cells	Anwar et al. (2020)

Table 1 (continued)

S. No	Target	Disease	IC50 (nM)	Assay description	Reference
17	Glycogen Synthase kinase 3 β	Alzheimer's disease	135	Inhibition of GSK-3 β enzyme involved in several human diseases	Paudel et al. (2018)

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of NF- κ B and STAT3 cascade activation and subsequent reduction of pro-survival genes. In addition to pleiotropic effects, RA inhibited pro-inflammatory cytokine release, thereby reducing colitis severity (Jin et al. 2017). In addition, researchers have detected that active ingredients of *Perilla frutescens* extracts, including apigenin, luteolin, and RA attenuated pro-inflammatory cytokine production, and RA specifically enhanced T-cell production, preventing dextran sulfate sodium (DSS) induced colitis in mice (Urushima et al. 2015). In another article on DSS-induced colitis models, RA and black-anthocyanin-rich extract alone or in combination alleviated inflammation through decreased myeloperoxidase and NO expression. In addition, reduced mRNA levels of IL-6, IL-1 β , and iNOS (Zhao et al. 2018). Surprisingly, polyethylene-coated RA-loaded nano-formulation mitigated colonic inflammation and palliates pro-inflammatory cytokine in the dextran sulfate sodium-induced acute colitis animal models. Similarly, RA-loaded chitosan/nutriose-coated niosomes enhanced downregulated NLP3 proteins, an adaptor protein, caspase-1, and reduced IL- β 1 levels in models of ulcerative colitis. On the other hand, RA enhanced Nrf2 translocation and hemeoxygenase expression exhibiting anti-inflammatory potential (Marinho et al. 2021).

Furthermore, the clinical efficacy of RA nano-formulation leads to an improved pharmacokinetic profile localized in the inflamed colon. However, the use of RA as therapeutic nano-medicine needs further consideration (Chung et al. 2020). Similarly, lipophilic modification of RA induces anti-colitic effects by activating the hypoxia-inducible factor 1-vascular endothelial growth factor pathway that improves ulcer healing (Jeong et al. 2015). Recently, Formiga et al. (2020) reported intestinal anti-inflammatory properties of RA in conjugation with p-Cymene. Combinatorial oral administration of RA and p-Cymene showed cytoprotective effects on trinitrobenzene sulphonic acid TNBS induced intestinal inflammation in rat models. This manifested as reduced mucosal injury and neutrophilic infiltrate. Both compounds exhibited immuno-modulatory effects by attenuating IL-1 β , TNF- α levels and modulating the T-cell population. Moreover, RA down-regulated NF- κ B transcription with subsequent induction of COX2 and iNOS. Few exciting research studies presented the gastro-protective effects of RA in ethanol-induced gastric lesions in vitro and in animal models. RA combated ulcer formation through modulation of oxidative parameters and inflammatory markers (do Nascimento et al. 2020; Wang et al. 2021b). Similar results were reported on ethanol-induced gastritis challenged rats. The RA-treated group showed increased antioxidant parameters and prostaglandin secretion, eventually protecting the mucosal barrier and gastric glands (Heidari et al. 2021). These findings corroborate and signify the general notion that RA possesses competent anti-inflammatory potential indicating that it can modulate inflammatory responses.

Given its anti-inflammatory attribute, RA exposure markedly increased inflammatory cells and Th2 cytokines in bronchoalveolar lavage fluid (BALF) with decreased total IgE and Ovalbumin (OVA) specific IgE levels and significantly improved airway hyperresponsiveness in OVA challenged the murine model of asthma (Liang et al. 2016). Histological findings reveal the presence of RA-mediated deranged mucus production and goblet cell hyperplasia. In another study reported by the same group, RA treatment significantly diminished inflammatory cells, upregulated SOD, glutathione peroxidase, and CAT activities, and a notable reduction in NOX-2 and NOX-4 expression in lung tissues. RA ameliorated oxidative lung injury and airway inflammation in asthmatic models (Liang et al. 2020). RA exhibited protective action against malathion (pesticide) induced lung damage through anti-inflammatory, antioxidant, and anti-apoptotic functions in albino Wistar rat models (Ahmed et al. 2021). However, future studies in vivo settings are required to unveil the underlying protective mechanism of RA. In another study, Shakeri et al. (2019) investigated the effects of RA on OVA-induced asthma and its influence on lung pathology of OVA-sensitized asthmatic rats. RA treatment significantly abridged IL-4, IgE, phospholipase A 2, and total protein levels but increased the IFN- γ /IL-4 ratio. Moreover, RA ameliorated pathological lung insults characterized by

diminished interstitial fibrosis, bleeding, epithelial damage, and interstitial inflammation.

RA has been found to prevent inflammation and lipid accumulation in adipocytes indicating anti-adipogenic potential. RA significantly reduced C/EBP α protein levels and marked a decrease of sterol regulatory-element binding protein-1 expression. In adipocytes, attenuation of the sterol regulatory-element binding protein-1 mediated pathway is associated with decreased IL-6, TNF- α , resistin, and adiponectin levels (Vasileva et al. 2021). Another study reported that RA suppressed peroxisome proliferator-activated receptor- γ and CCAA/enhancer-binding protein, which is α T mediated. Additionally, RA halted TNF- α mRNA levels and activated p-ERK1/2 and pSmad3, exerting an inhibitory effect on adipogenesis, lipolysis, and inflammation. These findings conclude that RA is a potential molecule for managing obesity-related inflammation.

RA showed protection in other inflammatory diseases such as periodontal disease, pancreatitis, neuropathy, ischemia, and allergic rhinitis. In gingival fibroblast, RA-based therapy quenched IL-1 β , IL-6, and TNF- α levels and inhibited iNOS. RA-based derangement of inflammatory response and improved anti-oxidant status alleviated progression of periodontitis. Also, RA pre-treatment was found to improve pathological alterations in sodium taurocholate-induced acute pancreatitis markedly and reduced

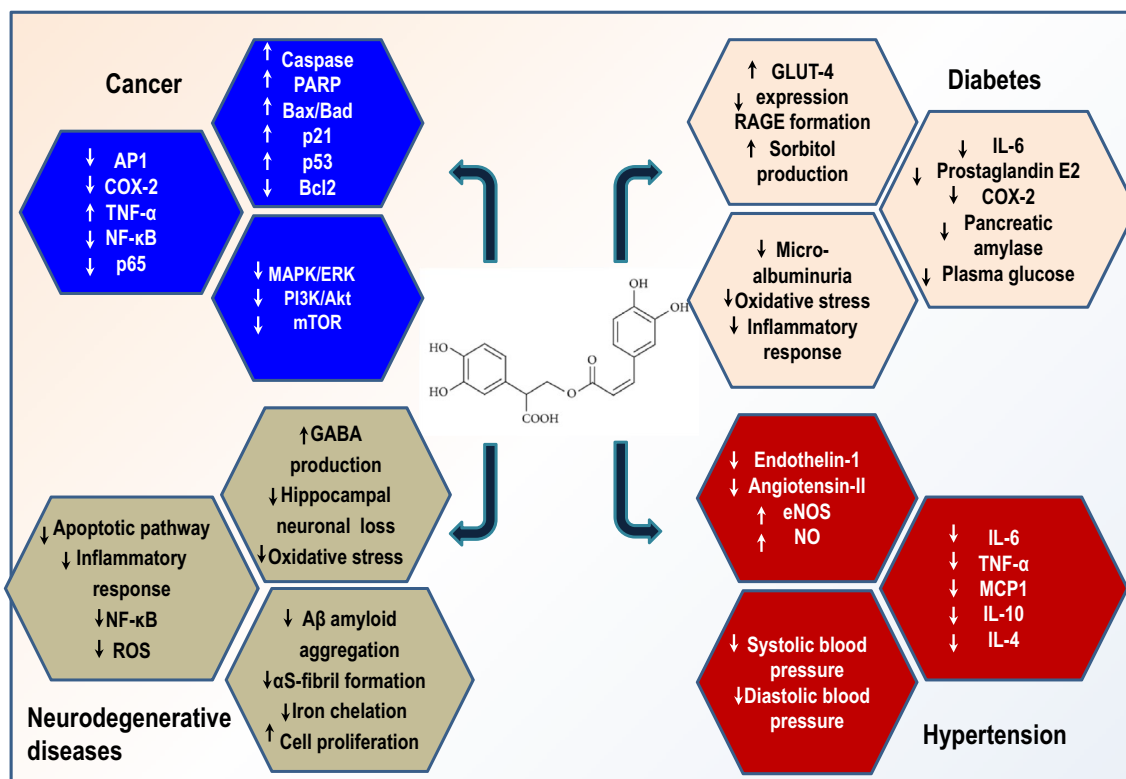


Fig. 2 Schematic diagram for possible mechanism of action of RA in ameliorating human diseases

inflammatory cytokine expression via downregulation of NF- κ B translocation (Fan et al. 2015) (Fig. 2). In another study, therapeutic effects of RA were investigated in inflammation-induced acute kidney disease in Swiss albino mice injected with cisplatin. RA administered at 100 mg/kg for two consecutive days blocked the NLRP3 signaling pathway. Consequently, RA treatment down-regulated NF- κ B and cyclooxygenase-2 expression and reduced renal tissue injury (Akhter et al. 2022). Similarly, RA diterpenes carsonic acid displayed effective countermeasures against acute and chronic COVID-19 complications and neurodegenerative diseases via inhibiting the NLRP3 inflammasome (Sato et al. 2022). Recently, Gonçalves et al. (2022) conducted a database search on Pubmed, Scopus, and Web of Science to evaluate the anti-inflammatory potential of RA in preclinical in vivo models of inflammation. The most evaluated biomarkers included myeloperoxidase, catalase, glutathione, glutathione peroxidase, malonaldehyde and superoxide dismutase. Intraperitoneal dose of 10 mg/kg showed anti-inflammatory activity before and after induction of treatment.

Anti-oxidant potential

Oxidative stress due to mitochondrial dysfunction can induce organ damage and aggravate inflammation. Persistent production of reactive oxygen species causes cellular oxidative stress, which strongly augments the development and progression of several diseases. Therefore, several anti-oxidant compounds from natural sources have been expansively investigated as alternatives to current treatment strategies. Sevgi et al. (2015) evaluated the anti-oxidant and DNA damage protection ability of ten different phenolic acids such as RA, caffeic acid, chlorogenic acid, etc. RA exhibited maximum potential in β -carotene bleaching, 2,2-diphenyl-1-picrylhydrazyl free radical scavenging, and chelating effect assays.

Studies have found that RA exhibits strong anti-oxidant capacity in biological systems by scavenging free radical and reactive oxygen species (Ghorbani et al. 2019; Kim et al. 2020a). Recently, Sadeghi et al. (2020) investigated the impact of RA on lipopolysaccharide-induced oxidative damage and inflammation in peripheral blood mononuclear cells. The study demonstrated RA-mediated decline in lipid peroxidation and NO levels and restored anti-oxidant/oxidant balance. Furthermore, RA ameliorated lipopolysaccharide-induced inflammation by alleviating NF- κ B and JNK MAPK signaling pathways. The beneficial role of RA in combating oxidative stress and associated diseases has been studied extensively. Tsai et al. (2019) showed protective effects of RA on selenite-induced cataract formation in Sprague–Dawley red pups. In addition, RA treatment significantly ameliorated oxidative damage by increasing

anti-oxidant status (Nrf2, SOD, HO1, NQO1) and anti-oxidant enzymes (GSH-Px, GSH-Rd, and catalase). Moreover, protein levels of filensin and calpain2 were escalated along with a reduction in lipid peroxidation, calcium, and inflammation. Shahrestani et al. (2021) investigated the protective effects of RA encapsulated with ZnO/chitosan nanoparticles on methamphetamine-induced oxidative stress damage and changes in casp3a mRNA levels in zebra fish. RA/ZnO/chitosan nanoparticles exhibited high efficiency in combating methamphetamine elevation in casp3a mRNA levels and oxidative changes. Ilhan et al. (2022) reported protective effects of azoxymethane-induced rat colon carcinogenesis and anti-oxidant/oxidant balance. Fuster et al. (2021) formulated RA-loaded silk-fibroin nanoparticles to investigate the anti-tumor potential in human cervical and breast cancer cells. The study concluded increased cellular uptake of modified RA and enhanced anti-tumor activity in HeLa and MCF-7 cell lines.

Similarly, combination therapy of RA with sinapic acid improved anti-oxidant parameters (superoxide dismutase and glutathione-related enzymes) and reduced lipid and protein peroxidation, thereby reducing oxidative damage in the lenses of estrogen-deficient rats (Zych et al. 2019b). Another article validated the anti-oxidative role of RA on the liver and kidney of aging mice. RA supplementation at a 200 mg/kg dose significantly escalated the anti-oxidant enzyme activity of catalase, superoxide dismutase, and glutathione peroxidase, decreasing malondialdehyde levels. Histopathological images showed significant structural alterations in liver and kidney tissues (Zhang et al. 2015). These findings conclude a possible role of RA therapy in preventing or slowing the oxidative stress-induced aging process.

In several reports, RA has acted as hepatoprotective agent through modulation of inflammatory cascades and oxidative imbalances (Luo et al. 2021; Touiss et al. 2021). RA has attenuated chromium-induced hepatorenal oxidative damage and the formation of preneoplastic lesions in rats through upregulation of the Nrf2 signaling pathway and antioxidant actions (Khalaf et al. 2020). Recently, hepatoprotective effects of RA on acetaminophen-induced acute liver damage in mice were reported. The underlying mechanism of action was the antioxidant effect mediated by RA through RACK1/TNF- α pathway (Yu et al. 2021).

Similarly, RA exposure showed remarkable effects of RA in alleviating hepatic steatosis, oxidative stress, inflammation, and apoptosis in mice model challenged with non-alcoholic steatohepatitis (Komeili-Movahhed et al. 2021). RA also provided significant protection from concanavalin A (reversible-competitive AMPK inhibitor) induced autoimmune hepatitis in mice. After RA treatment, Serum levels of pro-inflammatory cytokines (IFN- γ , IL-2, IL-1 β) were reduced, whereas anti-inflammatory cytokine (IL-10) was elevated. Furthermore, RA reduced hepatic damage via the

activation of AMPK signaling (Wang et al. 2020). Another study found that RA markedly reduced Sertoli cell damage in rats caused by the electromagnetic field. The results showed that RA significantly improved testosterone levels, total anti-oxidant capacity, decreased malondialdehyde, and Sertoli cell apoptosis. These results support the view that RA administration as a food supplement could be a preventive measure against electromagnetic field-induced damages (Hajhosseini et al. 2013).

Oxidative damage is the causative factor for cognitive dysfunction in neurological disorders. Some researchers have demonstrated that incorporating RA as a dietary supplement could improve neurological issues and restore cognitive functions (Hassanzadeh-Taheri et al. 2021). Hasanein et al. (2017) reported ameliorative effects of RA in an animal model of ethanol-induced cognitive impairment. Prolonged and dose-dependent RA supplementation improved cognitive deficits in the alcoholic group. Decreased lipid peroxidation and nitrite levels disturbed oxidant/anti-oxidant levels have been suggested as a possible mechanism of chronic ethanol-induced amnesia. These results indicate RA as a potential therapeutic agent against alcoholic dementia.

Similarly, the beneficial effects of RA were evaluated in 4-aminopyridine and picrotoxin-induced epileptic seizures in mice. Although RA exposure could not prevent seizures, it decreased reactive oxygen species levels, catalase, and superoxide dismutase activity. DNA damage was measured in hippocampal tissues. The potential of RA in combating DNA damage and protection against ethanol-induced genotoxicity has already been reported. In addition, mitochondrial complex II activity was also found to be elevated post RA treatment. Since mitochondrial dysfunction due to deranged respiratory chain complexes is associated with seizure-induced brain damage, RA mitigated in epileptic models. Several studies have previously indicated the neuroprotective effect of RA due to its free radical scavenging properties and the ability to modulate mediators of signaling cascade such as NF- κ B and *c-fos* that lead to neuronal apoptosis (Ma et al. 2020a). The study indicated that RA could exert anti-oxidant and neuroprotective effects in the treatment of epilepsy. Thus, RA could be incorporated with current anti-epileptic drugs in treating seizures (Luft et al. 2019). In another study, RA prevented oxidative stress and neuroinflammation in chemotherapy-induced peripheral neuropathy models. Dysregulated mitochondria aggravate oxidative stress that promotes an ongoing cycle of inflammatory damage.

Furthermore, an abrupt release of inflammatory cytokines can damage electron transport chain complexes, decrease ATP production and alter mitochondrial membrane potential. RA supplementation enhanced ATP production, restored mitochondrial membrane potential, tapered pro-inflammatory cytokine release, inhibited MAPK, and

maintained AMPK levels, thereby exhibiting mitoprotective properties. A recent finding postulated bactericidal activity of RA to prevent MRSA pneumonia through modulation of Keap/Nrf2 signaling cascade. RA is a known inducer of Nrf2, inhibits its proteasomal degradation, and promotes nuclear translocation (Zhang et al. 2021b). Few studies have reported the bacteriostatic effects of RA treatment (Lu et al. 2021). However, in-depth in vivo screening of RA for translational success in clinical settings are needed (Areti et al. 2018).

Clinical implications of RA

RA shows various remarkable biological activities that reduce the likelihood of developing metabolic diseases such as cancer, diabetes, and neurodegenerative disorders (Feng et al. 2020). Several research groups have investigated the health benefits of RA and its extracts. Few studies depicting the pharmacological functions of RA have been summarized in Table 2. The subsections below provide the recent updates on the therapeutic benefits of RA in combating some common metabolic disorders.

Anti-cancer potential

Cancer, also called malignant tumor or neoplasm, is a large group of diseases characterized by the rapid creation of abnormal cells with uncontrolled proliferation (Kim et al. 2009, 2021c; Hwang et al. 2011; Son et al. 2013; Chung et al. 2015; da Silva et al. 2021). The ability of malignant cells to evade apoptosis or programmed cell death results from mutations in signaling pathways regulators. According to recent estimates released by WHO, 19.3 million new cases worldwide were diagnosed in 2020, with 10 million deaths. The global burden is expected to be 28.4 million cases in 2040. Socio-economic status and the aging population remain the primary factors responsible for increased cancer cases. Several medicinal properties, including anti-cancer activities, have been attributed to RA. Repeated use of chemotherapy drugs and radiotherapy often induces chemo-resistance that causes cytotoxicity to normal cells. Identifying novel therapeutic compounds of natural origin has gained scientific attention as anti-cancer agents (Jin et al. 2020; da Silva et al. 2021).

Numerous evidences suggest anti-proliferative and pro-apoptotic effects of RA on cancer cells (Luo et al. 2020b; Pagano et al. 2021). RA downregulated DSS-induced colitis-associated colon cancer by propitiating TLR4/NF- κ B/STAT3 activation in murine model. RA significantly ameliorated colitis severity, inflammatory markers, and anti-apoptotic factors (Jin et al. 2021a). Anti-cancer effects of RA in prostate cancer cell lines were investigated. RA decreased cell

Table 2 Studies depicting various pharmacological functions of RA

S. No	Pharmacological role	Function	Reference
18	Anti-inflammatory	<ul style="list-style-type: none"> i. Reduced T-cell population, Bcl2 production in subjects with rheumatoid arthritis ii. Deranged inflammatory responses and improved acute pancreatitis in rat models iii. Decreased IgE production, mucus production and improved airway hyper-responsiveness in OVA-challenged asthmatic rats iv. In conjugation with p-Cymene, modulated inflammatory cascade and reduced TNBS- induced intestinal inflammation in acute colitis rat models v. Ameliorated inflammation induced renal injury via inhibition of NLRP3 signaling in Cisplatin injected Swill abino mice 	<p>Hur et al. (2007) Fan et al. (2015) Shakeri et al. (2019) Formiga et al. (2020) Akhter et al. (2022)</p>
19	Anti-oxidant	<ul style="list-style-type: none"> i. Slowed oxidative stress induced liver and kidney damage by enhancing anti-oxidant enzymes in mice models ii. Improved cognitive deficits in alcoholic dementia by reducing lipid peroxidation, nitrite levels and improving anti-oxidant status in rats iii. Ameliorated oxidative damage and exhibited protective effects in selenite-induced cataract animal models iv. Reduced acetaminophen-induced acute liver damage in mice through modulation of RACK1/TNF-α pathway v. Protective effects on methamphetamine-induced oxidative stress damage and changes in casp3a mRNA levels in zebra fish model 	<p>Zhang et al. (2015) Hasanein et al. (2017) Tsai et al. (2019) Yu et al. (2021) Shahrestani et al. (2021)</p>
20	Anti-cancer	<ul style="list-style-type: none"> i. Induced prostate cancer cell apoptosis via modulation of intrinsic mitochondrial apoptotic pathway mediators ii. Inhibited proliferation and invasion in hepatocellular carcinoma cells via targeting PI3K/Akt/mTOR signalling pathway iii. Blocked FOXO1 transcription factors, upregulated pro-apoptotic genes and exhibited anti-tumorigenic actions in triple negative breast cancer cells iv. Reduced pancreatic ductal adenocarcinoma via G1/S cycle arrest and inhibition of Gli translocation in mouse model of PDAC v. Propitiated TLR4/NF-κB/STAT3 activation and reduced colitis induced colon cancer in murine model 	<p>Jang et al. (2018) Wang et al. (2019) Messeha et al. (2020) Zhou et al. (2022) Jin et al. (2021a)</p>
21	Anti-diabetic	<ul style="list-style-type: none"> i. Exhibited protective role via anti-inflammatory action in diabetic cerebral ischemic damage ii. Ameliorated hyperglycemia and insulin resistance by altering phosphoenol pyruvate carboxykinase levels and enhancing GLUT-4 expression iii. Prevented podocyte injury, reduced microalbuminuria and improved kidney function in rats with diabetic nephropathy iv. Attenuated inflammatory response and type 1 diabetes development in mice via modulation of innate and adaptive immune response v. Prevented podocyte injury, diabetic nephropathy alone and more efficiently in combination with Telmisartan in rat models 	<p>Luan et al. (2013) Runtuwene et al. (2016) Samsu et al. (2019) Koprivica et al. (2022) Samsu et al. (2019)</p>
22	Anti-neurodegenerative	<ul style="list-style-type: none"> i. Attenuated motor neuron degeneration in rat models of amyotrophic lateral sclerosis ii. Enhanced dopamine signalling pathway and suppressed Aβ aggregation in AD mice models iii. Prevented degeneration of nigrostriatal dopaminergic system, inhibited iron-induced α-synuclein aggregation against MPTP induced neurotoxicity iv. Regulated DJ-1/Akt/Nrf2 signaling and combated MPTP-induced neurotoxicity in zebrafish model of PD v. RA-chitosan nano-conjugates improved memory, neuroinflammation in Wistar rats 	<p>Shimojo et al. (2010) Hase et al. (2019) Qu et al. (2019) Zhao et al. (2020) Fachel et al. (2020)</p>
23	Anti-hypertensive	<ul style="list-style-type: none"> i. Inhibited angiotensin-converting enzyme, reduced lipid profile, improved insulin sensitivity and lowered blood pressure in rats ii. Reduced vascular damage and blood pressure via inhibition of angiotensin-converting enzyme and pro-inflammatory cytokine release iii. Attenuated angiotensin converting enzyme and decreased hypertension in rats iv. Attenuated systolic blood pressure, increased eNOS production, improved vascular function in hypertensive rats 	<p>Karthik et al. (2011) Alegría-Herrera et al. (2019) Ferreira et al. (2018) Pantam et al. (2019)</p>

proliferation halted colony and spheroid formation in OC3 and DU145 cell lines. Furthermore, RA induced early and late-stage apoptosis downregulated proliferating cell nuclear antigen, cyclin, D1, and cyclin E1, whereas it upregulated p21 expression. In addition, RA supplementation inhibited a histone-deacetylase enzyme that modulated the expression of intrinsic mitochondrial apoptotic-pathway related genes (Bax, bcl-2, caspase-3, and poly ADP ribose polymerase 1) via enhancement of p53 levels. However, further in-depth studies are required to evaluate RA-mediated cytotoxicity on normal cells (Jang et al. 2018). In another study, the anti-cancer effects of RA on hepatocellular carcinoma were investigated. The findings demonstrated that dose-dependent RA induced G1 arrest and apoptosis and inhibited the epithelial to mesenchymal transition of SMMC-7721 cells (Fig. 2). Additionally, RA treatment markedly decreased tumor growth and phosphorylated-phosphoinositide 3-kinase (PI3K), p-Akt, and phosphorylated-mammalian target of rapamycin (p-mTOR) expression levels. This leads to the suggestion that RA-mediated anti-tumorigenic role may be partially achieved via inhibition of PI3K/Akt/mTOR pathway. The above results provide the theoretical basis for considering RA as an anti-cancer agent (Wang et al. 2019).

Similarly, RA exhibited anti-proliferative and pro-apoptotic functions by DJ-1 inhibition via regulation of the PI3K-Akt signaling pathway in osteosarcoma cells (Ma et al. 2020b). In triple-negative breast cancer cells, RA altered the expression of genes involved in intrinsic and extrinsic apoptotic pathways. Noticeably, RA exposure upregulated pro-apoptotic gene BNIP-3, TNF- α , and GADD45A, causing S phase arrest and suppressing surviving protein BIRC5 and TNFRSF11B (Messeha et al. 2020). Another report concluded that RA mediated the inhibition of melanoma cell proliferation, migration and invasion and promoted apoptosis by ameliorating ADAM17/EGFR/AKT/GSK3 β axis (Huang et al. 2021). The above findings reveal that PI3K-Akt signaling is a crucial biological target for RA in cancer cells (Lee et al. 2018a, 2018b; Ko et al. 2019; Park et al. 2020; Kim et al. 2020b, 2021a). On the contrary, in another study, RA acted as a radioprotector in healthy cells but caused significant damage to melanoma cells in irradiated cultures. The underlying mechanism could be RA-mediated eumelanin synthesis consuming intracellular glutathione inducing oxidative damage (Olivares et al. 2020).

RA exhibited chemo-preventive effects alone and combined with Paclitaxel drug in breast cancer mice models. RA significantly suppressed NF- κ B, VEGF, TNF- α expression and restored P53, Bcl-2, Bax, and caspase-3 levels, causing apoptosis (Mahmoud et al. 2021). Interestingly, in another study, Zhou et al. (2022) reported RA-based reduction in pancreatic ductal adenocarcinoma by restraining Gli translocation and facilitating proteasomal degradation. In addition, RA induced G1/S cell cycle arrest and apoptosis in the pancreatic ductal adenocarcinoma cells by regulating apoptotic genes'

expression. In Swiss BALB mice, RA exposure displayed protective effects in cisplatin-induced ovarian toxicity through modulation of anti-oxidant and anti-inflammatory parameters (Gui et al. 2021). RA exposure ameliorated doxorubicin-mediated cardiotoxicity in both in vitro and in vivo models and, therefore, also be a promising drug for combating anti-cancer drug-mediated toxicity (Rahbardar et al. 2021). Similar outcomes of RA pretreatment were reported on human cardiomyocyte cell lines and human-induced pluripotent stem-cell-derived cardiomyocytes exposed to doxorubicin.

RA significantly reduced doxorubicin-induced cell apoptosis and caspase9 activity. Furthermore, RA promotes hemeoxygenase expression and downregulated ROS production, displaying potential in combating cancer-therapy-related cardiac dysfunction (Zhang et al. 2020a). RA-mediated inhibition of NLRP3 inflammasome has been beneficial in cyclophosphamide triggered premature ovarian failure. The above findings reveals the mechanistic insights of therapeutic action of RA through inhibition of NLRP3 inflammasome and associated signalling pathway (Yao et al. 2020).

Repeated usage of chemotherapeutic drugs in clinical practice confers multidrug resistance (MDR) and harmful outcomes. Interestingly, RA acid methyl ester, a derivative of RA-induced therapeutic effects against cervical cancer, has been documented through transcriptome analysis. RA treatment downregulated oncogenic transcription factor forkhead box M1 (FOXM1) and target genes associated with abnormal cell proliferation and tumor growth. Moreover, combination treatment of cisplatin and RA methyl ester reversed the cisplatin resistance in ovarian cancer cells via possible inhibition of FOXM1 (Lim et al. 2020). Similarly, RA exposure alleviated MDR, increased Adriamycin and P-glycoprotein intracellular accumulation, and decreased MDR-1 gene transcription in gastric cancer cells (Li et al. 2013). Liao et al. (2020) investigated the potential of RA in reversing multidrug resistance in non-small cell lung cancer. These results postulate RA as a potent multidrug resistance reversal compound that induces remarkable apoptosis in non-small cell lung cancer (NSCLC) and G1 phase cell cycle arrest. The collective findings also provide evidence of a mechanistic link between RA and mitogen-activated protein kinase (MAPK) signaling, indicating RA as a potential drug for NSCLC treatment.

Ample evidence suggests RA's attenuating effects on morphological features of cancer cells, including invasion, metastasis, and angiogenesis (Hsieh et al. 2020). Mostly cancer cells represent altered glycosylation profiles with sialylated moieties and carbohydrate antigens. Recently, Radziejewska et al. (2018) reported RA administration's effect on gastric cancer's intrinsic characteristics and found that RA at 200 μ M concentration showed an inhibitory effect on sialylated Tn antigen expression matrix-metalloprotease 9 activity and enhanced collagen type 1 expression. Similarly, RA inhibited epithelial to

mesenchymal transition in metastatic colorectal cancer cells via p-38/AP1 signaling. The study also documents the involvement of mir-1225-5p expression in RA-mediated anti-metastatic potential (Yang et al. 2021). Another previous study conducted by Zhang et al. (2018) reported substantial changes in ovarian cancer cell morphology comprising appearance of cell surface projections, blebbing of the cell membrane, and formation of apoptotic bodies upon RA treatment. In addition, suppressed cell migration, chromatin condensation, and DNA fragmentation were also observed (Zhang et al. 2018). These results suggest the clinical usefulness of RA as a complementary compound supporting conventional cancer treatment by targeting pathological characteristics of tumor cells. Recently, our lab reported the anti-cancer effects of RA on neuroblastoma cells via microtubule affinity regulating kinase 4 (MARK-4) inhibition, a potential drug target in many cancers. Molecular docking and *in-silico* simulation analysis revealed excellent binding affinity of RA with active pockets of MARK-4, quenching its tau phosphorylation activity. The study reveals the mechanistic insights of RA-mediated therapeutic cancer management (Anwar et al. 2020). Previous literature documents the remarkable effects of RA in reducing tau phosphorylation and cognitive dysfunction via downregulation of the JNK signaling pathway (Yamamoto et al. 2021).

Interestingly RA has also been combined with siRNA therapy to detect its anti-apoptotic effects on human glioma cells. The heat shock protein (Hsp)-27 expression was attenuated with Hsp-siRNA alone with no significant apoptosis. However, combined treatment of RA and quercetin along with Hsp-siRNA transfection suppressed Hsp27 expression and enhanced caspase-3 activity, indicating RA to be a potent combinatorial agent for glioblastoma therapy (Şengelen and Önay-Uçar 2018). Liu et al. (2021) reported anti-apoptotic effects of RA on the human glioma cell line through inhibition of Fyn kinase. In addition, RA significantly reduced MMPs expression, cell invasion, and migration. In another study, RA in conjugation with anti-MUC1 antibody significantly inhibited biomarkers including Tn, sialylated Tn, and fucosylated sugar antigens in gastric cancer cells.

Moreover, RA and anti-MUC1 antibody's combined action enhanced pro-apoptotic proteins Bax and Bad with the reduction in anti-apoptotic marker Bcl2 mRNA expression (Radziejewska et al. 2021). RA's anti-tumor effects were demonstrated by a combination of Adriamycin on hepatocellular carcinoma cells. The synergistic effect of RA and Adriamycin enhanced apoptotic rates by triggering mitochondrial-mediated signaling pathways and alleviated DNA damage. The protective effects of RA on radiation-induced pulmonary fibrosis were investigated in rat models. RA-downregulated NF- κ B expression and modulated inflammatory markers. Furthermore, RA upregulated RhoA/

Rock signaling by upregulation of miR-19b-3p, inhibiting fibrosis (Zhang et al. 2020b).

Anti-diabetic potential

Diabetes mellitus is an endocrine disorder resulting from absolute or relative loss of insulin secretion and insulin resistance. Persistent hyperglycemia may lead to secondary organ damage in diabetes, causing retinopathy, nephropathy, neuropathy, and vascular diseases. Recently RA has gained pharmacological importance due to its anti-diabetic potential. Current anti-diabetic drugs have certain limitations in efficacy and safety, causing weight gain or sudden hyperglycemia (Ngo et al. 2018). Previous experimental evidence showed that RA treatment could alleviate diabetes-associated secondary complications (Rao et al. 2014).

Runtuwene et al. (2016) investigated the anti-diabetic role of RA on glucose homeostasis and insulin sensitivity in animal models with streptozotocin (STZ) induced type 1 diabetes and high fat-induced type 2 diabetes. The data suggest that RA ameliorated hyperglycemia and insulin resistance with decreased phosphoenolpyruvate carboxykinase expression in the liver and enhanced GLUT-4 expression in skeletal muscles. Interestingly, the study found that 200 mg/kg was the most effective RA dose to exhibit anti-diabetic potential. A similar dose of RA has been used in other studies; however, clinical trials should be conducted to evaluate the effectiveness in humans with diabetes mellitus. In another research, type1 diabetic mice model, phenylethyl ester of RA attenuated inflammatory response and type 1 diabetes development through specific interference with innate and adaptive immune responses (Koprivica et al. 2022). Another study validated enhanced glucose uptake in skeletal muscles at 2 μ M RA concentrations. In this study, RA-mediated glucose uptake was PI3K/Akt independent as wortmannin (inhibitor of PI3K) did not modulate RA stimulated glucose uptake. Interestingly, RA inhibited DNA-glycation, thereby modulating Akt-1 and Akt-3 expression in the hippocampal region of STZ-induced diabetic rats (Alrubaye et al. 2021).

Additionally, AMPK phosphorylation was also increased; however, more profound insights into the underlying mechanism of RA in the regulation of glucose homeostasis need to be explored (Vlavcheski et al. 2017). Studies have also reported the inhibitory effect of RA on pancreatic amylase. As pancreatic amylase inhibitors are considered a good option for treating hyperglycemia by preventing glucose release from starch, these inhibitors can be utilized as anti-diabetic drugs (McCue and Shetty 2004).

Many scientific kinds of research have shown that RA and related constituents significantly improved glucose and lipid metabolism, oxidative parameters, and inflammatory status (Michalikova et al. 2021). Oxidative damage and inflammation play a crucial role in the pathophysiological

mechanism of diabetes mellitus exerting harmful effects leading to progressive organ damage. The pharmacological effects of RA have been studied in combating diabetes micro-vascular and macro-vascular complications (Bao et al. 2020). In a recent study, RA supplementation improved oxidized lipid-induced endothelial dysfunction in diabetic atherosclerosis via regulation of the p38-FOXO1-TXNIP signaling pathway and inhibition of NLRP3 inflammasome formation (Nyandwi et al. 2020). Uncontrolled hyperglycemia increases the possibility of ischemic stroke, and NF- κ B activation plays a pivotal role in diabetic stroke pathogenesis. Some researchers have documented neuroprotective effects of RA via blockade of inflammatory response. Luan et al. (2013) explored the neuroinflammatory potential of RA against diabetic cerebral ischemic damage. RA attenuated BBB degradation, decreased infarct volume, reduced HMGB1 expression, and enhanced NF- κ B and IF- κ B- α phosphorylation during diabetic cerebral ischemic injury. These findings indicate the anti-inflammatory potential of RA as a therapeutic drug in diabetic cerebral ischemic injury. Another group of researchers explored the protective role of RA in hepatic inflammation in the diabetic state. It examined the impact of RA on inflammatory stress in the liver of type 1 diabetic mice. RA supplementation alleviated diabetes progression, hepatic inflammation, and glycation stress via decreased levels of IL-6, prostaglandin E2, and cyclooxygenase-2 enzyme (Fig. 2).

Moreover, RA treatment markedly reduced receptors for the formation of advanced glycation end products formation and enhanced hepatic sorbitol production, consequently diminishing glycative stress. These results suggest that RA may ameliorate hepatic inflammation and glycative injuries under a diabetic state by regulating inflammatory cascades and polyol pathways (Wen and Yin 2017). Oxidative stress significantly contributes to diabetes mellitus that several anti-oxidants can reduce. According to a study, RA exerts anti-inflammatory effects and improves endothelial function (Sotnikova et al. 2013). In concordance with the above study, Sotnikova et al. (2015) investigated the effect of RA treatment on systemic oxidative stress in STZ-induced diabetic rats. RA administration (50 mg/kg) mitigated oxidative stress-induced tissue injury in the kidney and pancreas. Consistent RA exposure for 10 weeks depressed lipid peroxidation and raised GSH levels to be normal.

Similarly, RA exhibited a hepatoprotective and renoprotective role in combating oxidative stress in STZ induced diabetic rats. RA did not show any effect in improving glycaemic levels; however, SOD and CAT, ascorbic acid, non-protein thiol, and delta-aminolevulinic acid dehydratase were increased in the liver and kidney of diabetic rats (Mushtaq et al. 2015). Similarly, RA treatment reduced methotrexate-induced hepatotoxicity and nephrotoxicity in the Wistar rat model. RA reduced necrosis and leukocyte infiltration

through antioxidant and anti-inflammatory characteristics (Jafaripour et al. 2021). Such reports prove that naturally occurring compounds may contribute to diabetes management. In another report, RA attenuated high glucose-induced mitochondrial injury and improved cardiac function in diabetic mice models with cardiomyopathy via activating the SIRT1/PGC-1 α pathway (Diao et al. 2021).

Samsu et al. (2019) observed the significance of RA monotherapy in preventing podocyte injury, detachment, and subsequent development of diabetic nephropathy in rats. It was found that treatment with RA alone was significantly more efficacious than the combination of telmisartan and RA in reducing microalbuminuria and improving kidney function. However, further studies are required to clarify the non-synergistic effects of RA and telmisartan in combination therapy. A group of researchers conducted a comparative analysis on hypoglycaemic, hyperlipidemic, and anti-oxidative effects of RA and another rosemary compound, carnosic acid. Both compounds showed anti-glycative, anti-oxidative roles, anti-inflammatory roles, and protected tissue damage. However, RA showed a stronger protective role than carnosic acid in alleviating diabetic symptoms (Ou et al. 2018). Another study evaluated the anti-oxidative effect of RA and sinapic acid in combination in type 2 diabetic rats (Zych et al. 2019a). The findings point to the beneficial impact of RA and sinapic acid treatment on oxidative stress parameters. Silva et al. (2021) demonstrated the hypoglycemic effect of RA extracts from *Origanum vulgare* on alloxan-induced diabetic. Diabetes is characterized by the deposition of amylin protein aggregates in pancreatic islets, contributing to diabetic pathology. RA oral administration prevented amylin aggregation, providing insight into RA's nutraceutical properties in diabetes management (Wu et al. 2021).

Anti-neurodegenerative potential

The progressive dysfunction and loss of a selectively vulnerable group of neuronal cells are classic neurodegenerative diseases (Kumar et al. 2016, 2022). Abnormal protein accumulation and deposition, such as neurofibrillary tangles, Lewy body, tau protein, and α -synuclein, constitute the major histological marker of neuropathologic diagnosis (Gibb and Lees 1988). Numerous in vivo and in vitro studies demonstrated that natural compounds with high anti-oxidative and anti-inflammatory properties might be essential in managing neurodegenerative diseases, including epilepsy, Alzheimer's disease (AD), Parkinson's disease (PD), memory impairment, and sclerosis (Ghasemzadeh and Hosseinzadeh 2020; Thingore et al. 2021). RA is well-known for combating ROS production and inflammatory response, highlighting its clinical significance in reducing neurodegenerative damage (Fachel et al. 2019). RA significantly abrogated LPS-induced mitochondrial dysregulation, oxidative/

nitrosative damage, and neuroinflammation by promoting microglial M1/M2 repolarization (Wei et al. 2021). In another group, RA showed protective effects against LPS-mediated neuroinflammation by exhibiting anti-inflammatory potential in the adult zebrafish model (Fasolo et al. 2021). Fachel et al. (2020) formulated RA-loaded mucoadhesive chitosan-coated nanoemulsions against LPS induced neuroinflammation and memory defect in Wistar rats. RA bioavailability was enhanced with improvement in neuroprotection. Previous reports have affirmed the implication of RA in promoting neurogenesis and alleviation of cognition defects and synaptic regulation (Mirza et al. 2021). RA has been proven to be a promising, innovative, and effective pharmacotherapy agent for treating depressive disorders (Lataliza et al. 2021). micro-RNAs play a pivotal role in the pathogenesis of neurodegenerative diseases. Lv et al. (2020) demonstrated RA-mediated regulation of mi-miR-155-5p alleviating PD pathogenesis and concluded that suggesting that miR-155-5p could be used as a target for PD therapeutic management.

RA administration from presymptomatic stage attenuated motor neuron degeneration improved clinical score and extended lifespan in rat models of amyotrophic lateral sclerosis (Shimojo et al. 2010). In a mice model with PTZ induced seizures, RA exposure improved latency and reduced seizure frequency, reinforcing the neuroprotective effect of RA in epilepsy (Coelho et al. 2015). Several studies have reported that RA can modulate the gamma-aminobutyric acidergic (GABA) neurotransmission system via attenuating GABA transaminase enzyme. RA exposure enhances GABA production in the synaptic cleft, resulting in increased GABA transmission and an attractive strategy for epilepsy treatment (Ben-Menachem 2011). Another study evaluated anticonvulsant, anti-oxidative, and neuroprotective effects of RA treatment in mice models of picrotoxin and 4-aminopyridine induced seizures (Luft et al. 2019). The findings demonstrated that RA significantly reduced neuronal cell damage and can be administered in conjugation with anti-epileptic drugs for improved outcomes (Fig. 2).

Several drugs targeting A β (amyloid β) gathering or reversals have failed clinical trials, demanding a timely search for polyphenolic compounds with anti-amyloidogenic properties. RA and its derivatives reduced protein aggregation in several neurological disorders, with immense preventive benefits (Lin et al. 2020). In this regard, Cornejo et al. (2017) investigated the anti-aggregating properties of some phenolic compounds, including RA, on heparin-induced tau aggregation in vitro. Structure-based analysis revealed that RA interacted with the hexapeptide region involved in fibrillization and β -sheet assembly and prevented tau-aggregation. Similarly, Hase et al. (2019) reported RA-mediated suppression of A β aggregation in AD mice models via enhancing dopamine

signaling pathway through inhibition of monoamine oxidase. *Salvia officinalis* extracts containing RA reduced A β induced neurotoxicity in cultured rat pheochromocytoma cells. RA also reduced subsequent events associated with A β toxicity, including oxidative stress, DNA fragmentation, and tau-hyperphosphorylation (Iuvone et al. 2006).

Another study reported that RA exerted protective effects on A β evoked oxidative stress via Akt/GSK-3 β /Fyn pathway through upregulation of nuclear factor E2-related factor (Nrf2) activity (Rong et al. 2018). Previous studies have reported the clinical effectiveness of RA-rich *Melissa officinalis* in preventing AD progression (Noguchi-Shinohara et al. 2020). The safety of RA (from *Melissa officinalis*) consumption was evaluated in a randomized-placebo controlled double-blind trial conducted for 24 weeks on subjects with mild dementia associated with AD. *Melissa officinalis* extract containing 500 mg RA was well tolerated by AD subjects with no adverse effects (Luft et al. 2019). The above findings could validate the implication of RA in the therapeutic management of AD. However, more comprehensive studies are needed to apply RA as a nutraceutical supplementation agent for AD treatment.

Derangement of dopaminergic neurons and dopamine production are classical neuropathological characteristics of PD. Additionally, increased oxidative markers and iron level-neuronal apoptosis are triggering factors. Hence compounds displaying multiple features, including iron-chelating, anti-apoptotic and free-radical scavenging, might serve as potential candidates for therapeutic management of PD. The ameliorative effects of RA on dopaminergic cell apoptosis and ROS production in PD have been evaluated in several studies. Wang et al. (2012) reported the neurorescue effect of RA on 6-hydroxydopamine (6-OHDA) induced dopamine neuronal cell toxicity in rat PD models. 6-OHDA treatment reduced dopamine in the striatum and increased nigral iron load and apoptotic mediators. RA rescued dopamine neuron degeneration, eliminated excessive iron-reducing redox activity, and regulated Bcl2-/Bax gene expression. The study indicates the potential application of RA as iron-chelators to encounter neurodegenerative diseases. The accumulation of α -synuclein in the brain is associated with several neurodegenerative disorders. RA has been extensively studied for its effects on the formation of α -synuclein fibrils and degradation of preformed α -synuclein aggregates. The studies concluded that RA displayed anti-oxidant and anti-fibrillogenic features and might be a key candidate for ameliorating PD and similar diseases. In this regard, protective effects of RA were studied against 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP) induced neurotoxicity on a mouse model of PD. RA could prevent degeneration of the nigrostriatal dopaminergic system by downgrading nigral iron levels, increasing SOD and tyrosine hydroxylase positive neurons.

Furthermore, RA exposure inhibited iron-induced α -synuclein aggregation via upregulation of hemoxygenase 1 and inhibited α -synuclein expression (Qu et al. 2019). Another study reported neuroprotective action of RA in MPTP-induced neurotoxicity in dopaminergic neurons of a zebrafish model of PD through regulating the DJ-1/Akt/Nrf2 signaling pathway (Zhao et al. 2020). These findings project mechanistic insights of RA-mediated attenuation in the development and progression of neurodegenerative disorders.

Moreover, RA amended depressive behavior in rats exposed to chronic unpredictable stress. The anti-depressant-like effect exerted by RA may be attributed to astrocytic BDNF expression in the hippocampal region via enhancement of ERK1/2 phosphorylation. However, further in-depth studies are needed to validate the detailed underlying mechanism of the anti-depressive properties of RA (Jin et al. 2013). Interestingly, in another study, RA exerted neuroprotective effects against focal ischemic stroke and post-stroke depression in vivo through augmenting anti-oxidant response (Wang et al. 2021c). As the reduction in glutamate release is crucial for neuroprotection, RA treatment significantly tapered glutamate release in concentration-dependent manner via activation of GABA_A receptors in cerebrocortical synaptosomes (Wang et al. 2021a). These findings propose that RA might motivate the future development of innovative anti-depressant drugs. However, more clinical studies are required to develop RA as an anti-depressant on depressing subjects.

Anti-hypertensive potential

As the data suggest, phenolic compounds like RA exhibited significant anti-hypertensive effects in-various studies, making it an alternative therapeutic agent for hypertension treatment (Kwon et al. 2006). Recently Karthik et al. (2011) evaluated investigated cardioprotective and anti-hypertensive effects of RA in fructose-fed rats. RA supplementation reduced lipid levels, improved insulin sensitivity, and lowered blood pressure by decreasing endothelin-1 and angiotensin-converting enzyme activity. Additionally, histopathological analysis revealed reduced myocardial damage through its anti-oxidant properties. RA supplementation displayed cardioprotective effects against myocardial ischemia/reperfusion (I/R) injury through amelioration of NF- κ B signaling pathway and ROS changes in male C57BL/6 J mice (Quan et al. 2021). In conjugation with extracts from *Ocimum basiculum* and *Ocimum selloi*, RA ameliorated angiotensin-II mediated damage and alleviated pro-inflammatory cytokines and macrophage chemotactic protein 1 levels (Alegría-Herrera et al. 2019). These findings suggest the multifaceted action of RA in blood pressure management and associated vascular damage.

Interestingly, RA derivative, ethyl rosmarinate, has been evaluated for effects on N^o-nitro-L-arginine methyl ester (L-NAME)—induced hypertensive rat models. The data indicated that ethyl rosmarinate significantly attenuated systolic blood pressure, increased eNOS production, and improved vascular function (Pantan et al. 2019). Another group of researchers studied the inhibitory effect of RA on angiotensin-converting enzyme activity and hypertension. RA treatment caused a dose-dependent decrease in systolic blood pressure in the hypertensive group and angiotensin-converting enzyme activity in rat lung tissue (Ferreira et al. 2018). Angiotensin-II is a potent agent that generates oxidative damage and hypertension. In concordance with previous studies, acute and chronic RA treatment attenuated angiotensin-II mediated rise in systolic, diastolic, and arterial blood pressure and cardio-metabolic abnormalities in rats (Fig. 2). In addition, acute RA reduced fasting plasma glucose and induced glucose transport activity in skeletal muscle. Therefore, it can be concluded that RA and its derivatives can be considered exciting candidates for alternative treatment against angiotensin-II associated hypertension and hyperglycemia (Prasannarong et al. 2019).

Pharmacokinetic profile of RA

The pharmacokinetic profile of RA was initially reported in animal models, including mice and rats, and later in humans (Hitl et al. 2021). Several studies investigated the pharmacokinetics of RA and later concluded that pharmacokinetic parameters differ in humans and animals (Nakazawa and Ohsawa 1998; Matsuno et al. 2002; Baba et al. 2005; Gamaro et al. 2011; Nunes et al. 2017). A study in healthy humans was performed to determine RA's absorption, metabolism, and urinary excretion. Six healthy men were enrolled in the study involving single intakes of perilla extract containing 200 mg RA and placebo with a 10-days interval. RA and its related metabolites methylated RA, caffeic acid, and ferulic acid was detected in the plasma and urine after intake of PE (Baba et al. 2005). The proportion of RA and its related metabolites excreted in the urine was $6.3 \pm 2.2\%$ of the total dose, with approximately 75% of these components being excreted within 6 h after the intake of perilla extract (Baba et al. 2005). Another study shows that RA was well absorbed from the gastrointestinal tract and the skin (al-Sereiti et al. 1999). The toxic effect of RA on inflammatory and nociception in rats indicated its non-toxicity compared with the control group (Gamaro et al. 2011). The pharmacokinetic properties of RA calculated through the pkCSM web tool (<http://biosig.unimelb.edu.au/pkcsm/>) are given in Table 3.

Table 3 Pharmacokinetic properties of RA calculated through pkCSM web tool

Absorption		Distribution	Metabolism	Excretion		Toxicity	
GI absorption	Skin Permeability (log Kp)	BBB/CNS permeability	CYP2D6 substrate/inhibitor	Clearance (log ml/min/kg)	Renal OCT2 substrate	AMES	Hepatotoxicity
Low	-2.73	No	No	0.25	No	No	No

Clinical trials on RA

Several herbal apothecaries have attributed the flora with various human health benefits. In this regard, two similar double-blind placebo-controlled crossover studies were performed to assess the effect of *M. Officinalis* extracts containing RA on cognitive functions and mood modulation in healthy young adults. The study concluded that foodstuffs containing lemon balm extracts might have positive behavioral effects, implied in clinical health settings (Scholey et al. 2014).

As described previously, RA is known to display anti-inflammatory and anti-oxidant potential. In this regard, the protective functions of RA were investigated on subjects with atopic dermatitis. Twenty-one subjects with atopic dermatitis were enrolled in the study. Topical application of RA (0.3%) emulsion improved skin dryness, pruritus, and general AD symptoms, indicating that RA can be incorporated as a therapeutic agent for atopic dermatitis treatment. However, the precise molecular mechanism of RA-mediated improvement in atopic dermatitis remains to be explored (Lee et al. 2008). A randomized, double-blind study investigated the anti-inflammatory effects of RA obtained from spearmint extracts on individuals with knee osteoarthritis. The findings reported significant improvement in mobility and stiffness in adults with knee osteoarthritis on daily high RA spearmint tea consumption for 16 weeks (Connelly et al. 2014).

Similarly, supplementation of spearmint extract rich in polyphenols, including RA, was investigated in a placebo study on cognitive functions, sleep pattern, and mood in human subjects with age-associated memory impairment. The study reported that consumption of 900 mg/day for 90 days improved working memory and spatial memory quality, sleep patterns, and mood status in subjects with age-associated memory impairment. Another similar trial reported that daily consumption of 900 mg of proprietary spearmint extract containing 14.5% RA and 24% total phenolic content improved reactive agility in the young population with no adverse effects (NCT02518165). These findings suggest the benefits of phenolic compounds, including RA, in individuals with memory impairment (Herrlinger et al. 2018). A study reported beneficial effects of RA in curing insomnia via hypnotic effects targeting A₁R agonists (Kim

et al. 2022). Few placebo-controlled trials have monitored the efficacy and safety of polyphenolic compounds for treating allergic inflammatory diseases. Takano et al. (2004) conducted a randomized, double-blind placebo-controlled study on subjects with mid-seasonal allergic rhinoconjunctivitis supplemented with extracts of *Perilla frutescens* enriched with RA. The RA supplemented group displayed attenuated polymorphonuclear leukocytes in the nostrils compared to the placebo group. No adverse events and significant abnormalities were observed upon RA administration. The above reports provide a comprehensive understanding of introducing phenolic compounds as alternative medicines in treating inflammatory diseases.

Dietary supplementation of *O. stamineus* RA enriched Nuvastatic TM (1000 mg) ameliorated oxidative damage restored mitochondrial and cellular functions bring down fatigue in subjects with solid stage I-IV tumors. Also, the neuroprotective effects of RA potentially deranged pain, sleep loss, lethargy, and other symptoms associated with cancer-related fatigue in Phase III (NCT04546607). In another trial, mint tea with high content of RA blunted chronic eosinophilic inflammation in adults with bilateral nasal polyps (NCT00465543). The safety and efficacy of RA treatment were compared to the placebo group receiving the inactive substance. Recently, a randomized, double-blind clinical study was conducted in Phase II on oral nutraceutical Lertal^R having RA as an active ingredient in conjugation with standard therapy (antihistamine) among children with allergic rhinoconjunctivitis. The polycentric study concluded that prolonged Lertal^R consumption significantly reduced allergic rhinoconjunctivitis exacerbation and reduced usage of rescue medications with no adverse events. Therefore, Lertal^R can be envisioned as an effective add-on treatment with standard therapy in allergic rhinoconjunctivitis in pediatrics (Marseglia et al. 2019) (NCT03365648).

Conclusion and future prospects

Ample evidences validate the potential benefits of RA as a nutraceutical and therapeutic candidate (Alavi et al. 2021). Pure RA-containing products are also available commercially. The diverse biological functions of phenolic compounds like RA can provide various health benefits (Özveren

et al. 2020). RA acts as a powerful anti-oxidant agent mitigating oxidative damage, which could reduce the induction of ROS production via the enhancement of anti-oxidant defense enzymes (Khamse et al. 2020). RA and its derivatives have been extensively investigated as pharmaceutical agents against several diseases, including cancer, diabetes, neurodegenerative disorders, hypertension, and inflammatory diseases (Shamsi et al. 2020).

From ancient times, RA has been used as anti-microbial, anti-fungal, and anti-allergic substance in several remedies. Due to its anti-oxidant and anti-inflammatory properties, RA has been an attractive chemotherapeutic agent and has effectively controlled tumors in various stages (Waer et al. 2020). RA has been beneficial in alleviating several pathological characteristics of neurodegenerative disease, including protein aggregation, iron chelation, neuronal apoptosis, and oxidative stress. RA balances the anti-oxidant/oxidant system, protecting the cell from ROS-mediated damage through its anti-oxidant properties. Further investigations are needed to explore the mechanistic insights of RA-mediated protective functions in various experimental models. Though several studies reported a lack of adverse effects upon RA intake, few recorded complaints, such as dry mouth, itchy scalp, abdominal discomfort, and headaches had been reported (Connelly et al. 2014). Hence, the complete pharmacokinetic profile of RA should be thoroughly explored to determine its safety and efficacy in healthy subjects.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare no conflict of interest.

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