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REVIEW ARTICLE

Concise Reviews and Hypotheses in Food Science

10-hydroxy decanoic acid, trans-10-hydroxy-2-decanoic acid, and sebacic acid: Source, metabolism, and potential health functionalities and nutraceutical applications

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Abstract

The popularity of royal jelly (RJ) as a functional food has attracted attention from various industries, especially nutraceuticals, due to the increasing demand from health enthusiasts. Sebacic acid, 10-hydroxy decanoic acid, and trans-10-hydroxy-2-decanoic acid are the primary medium-chain fatty acids (MCFAs) within RJ responsible for their health benefits. This review aims to consolidate information on these MCFAs' metabolic relationship and health functionalities in nutraceutical applications. We also investigated the natural characteristics mediated by these MCFAs and their metabolism in organisms. Finally, the production of these MCFAs using conventional (from castor oil) and alternative (from RJ) pathways was also discussed. This review can be a reference for using them as functional ingredients in nutraceutical industries.

KEYWORDS

10-hydroxydecanoic acid, health functionalities, royal jelly, sebacic acid, trans-10-hydroxy-2-decanoic acid

1 | INTRODUCTION

Royal jelly (RJ) has been utilized in conventional medicine since the beginning of civilization, especially in ancient Egypt and Asian apitherapy (Moţ, 2015). However, consumer and food industry interest in healthy natural goods to prevent sickness and advance health has gradually increased over the past few years (Chen et al., 2016). RJ is among the most alluring functional compounds employed in various industries, including nutraceuticals, pharmaceuticals, and cosmetics, because of its exceptional biological qualities (Chen et al., 2016).

It has been established that RJ's nutrients and functional substances are responsible for their pharmacological properties (Chen et al., 2016). The lipids in RJ are saturated and unsaturated straight-chain fatty acids with terminal and internal hydroxylation, terminal mono- or dicarboxylic acid function, and saturated or unsaturated branched

dibasic acids (El-Guendouz et al., 2020). Most lipid fractions are functional medium-chain fatty acids (MCFAs), of which 10-hydroxy decanoic acid (10-HDAA) makes up 22% and trans-10-hydroxy-2-decanoic acid (10-H2DA) and sebacic acid (SA), taken together, comprise 36% (Terada et al., 2011). Generally, fatty acids produced by lipolysis are catabolized via the mitochondrial fatty acid β-oxidation pathway to meet the energy requirements of cellular metabolism (Bülow et al., 2018). However, both exogenous and endogenous 10-HDAA, 10-H2DA, and SA do not only function through the general lipid metabolism pathway but also as physiologically active substances (Althobaiti, 2022).

Recent studies hypothesized that many of the RJ's biological characteristics (neurotrophic activity, estrogen-like activity, antioxidant activity, anti-inflammatory activity, anti-tumor activity, glucose-regulating activity, and antimicrobial activity) are contributed by 10-HDAA, 10-H2DA, and SA unique to RJ (Chen et al., 2016). Various studies have investigated the biological properties of SA, 10-H2DA, and 10-HDAA for use in the nutraceutical and pharmaceutical industries. Moreover, owing to the beneficial biological activities and high application value, researchers have explored their synthesis routes and extraction techniques. This review aimed to gather findings on the biological properties of SA, 10-H2DA, and 10-HDAA in the progress of studies in the nutraceutical industry. This review also investigated the natural characteristics mediated by these substances, their metabolism in the organism, and their alternative source pathways.

2 | SA, 10-H2DA, AND 10-HDAA

2.1 | Sources of SA, 10-H2DA, and 10-HDAA

Due to numerous allergy symptoms following the first RJ intake, cross-reactive allergens have long been hypothesized (Hata et al., 2020). The isolation of functional components of RJ is one of the effective methods to make it more widely used, reduce its allergenicity, and improve the efficiency of product utilization. In recent years, SA, 10-H2DA, and 10-HDAA have been RJ's most researched functional components, attracting much scientific attention (Chen et al., 2016). The most prevalent fatty acid and a significant lipid component of RJ is 10-H2DA. Although 10-H2DA can be obtained by RJ extraction, producing 10-H2DA by synthetic methods is of high purity, good efficiency, and more manageable quality assurance. No less than 10 synthetic routes were reported, mainly divided into chemical synthesis and biosynthesis methods (Li et al., 2022).

The microbial synthesis of 10-H2DA has emerged as a superior substitute for conventional production methods in recent times (Fang et al., 2024). Key enzymes, such as cytochrome P450 (CYP), acyl-coenzyme A synthetase, acyl-coenzyme A dehydrogenase, and acyl-coenzyme A thioesterase, can be employed with *Escherichia coli* to synthesize 10-H2DA. The enzyme acyl-coenzyme A synthetase catalyzes the conversion of fatty acids into acyl-coenzyme A and exhibits a broad range of substrate specificity (Fang et al., 2024). The acyl-coenzyme Enoyl-coenzyme A is formed via the desaturation of the carboxyl β-position of acyl-coenzyme, which is catalyzed by a dehydrogenase. The acyl-coenzyme *Pseudomonas putida* KT2440's dehydrogenase changes decanoic acid into trans-2-decenoic acid (Li et al., 2022). In addition to their primary function of oxidizing the C–H bond, CYP enzymes are found in many organisms. These enzymes carry out hydroxylation, epoxidation, and hetero-oxidation (Gregson et al., 2019). By generating 10-HDAA from decanoic acid and 10-H2DA from trans-2-decenoic acid, they can efficiently hydroxylate medium-chain saturated and long-chain monounsaturated fatty acids. However, the yield of 10-H2DA is affected by a high concentration of decanoic acid. Moreover, the substrate conversion rate and product concentration are limited by the inhibitory activity of 10-H2DA on the strain and its low solubility in the cell, that is, less than 0.1 g per 100 g of water (Fang et al., 2024).

Further, a study by Jeon et al. (2019) has genetically engineered a diploid *Candida tropicalis* yeast, which is impaired in β-oxidation, and created an effective microbial cell factory that can produce SA from a vegetable oil-derived source by overexpressing genes involved in hydrocarbon ω-oxidation. Recent studies point out that SA, 10-H2DA, and 10-HDAA are toxic to microorganisms for induced production, demanding production conditions, lack of continuity in the reaction, low conversion rates, which can lead to accumulation of intermediates, and poor stability of genetically engineered bacteria, among others (Fang et al., 2024; Jeon et al., 2019).

For safety reasons, SA, 10-H2DA, and 10-HDAA obtained by chemical synthesis and biosynthesis methods are rarely used in the food industry (Table 1). SA is rarely ingested because it is almost absent in food commonly consumed but is present in deficient levels of honey (Shirakawa et al., 2020). However, recent studies have found that SA accounts for ~22% of the lipid extract of RJ (Xu et al., 2009). Generally, SA is a natural substance produced by organisms through fatty acid oxidation (Chen et al., 2016). In animals and humans, long-chain dicarboxylic acids are always β-oxidized to create SA. However, only traces are produced (Ranea-Robles et al., 2021). Although some scientists have extracted SA from RJ, the extraction efficiency is not high, and the applications

TABLE 1 Source summary for sebacic acid (SA), 10-hydroxydecanoic acid (10-HDAA), and trans-10-hydroxy-2-decanoic acid (10-H2DA).

Substances	Methods	Sources	References
SA	Chemical synthesis	Ricinoleic acid	Group (2016)
	Biosynthesis	Strains (substrates:vegetable oil and glucose)	Jeon et al. (2019)
	Extraction	Royal jelly	Liu et al. (2015)
10-H2DA	Chemical synthesis	Ricinoleic acid	Feng et al. (2017)
	Biosynthesis	Strains (substrates:decanoic acid)	Fang et al. (2024) and Sun (2019)
	Extraction	Royal jelly	Xu et al. (2009)
10-HDAA	Chemical synthesis	Ricinoleic acid	Li and Huang (2011)
	Biosynthesis	Strains (substrates:decanoic acid)	Fang et al. (2024)

are fewer. The primary production method is still the castor oil cracking reaction. Similarly, 10-HDAA is present in RJ. But there are no reports on its natural extraction. In industrial production, 10-HDAA can be produced by high-temperature cracking of glycerol ricinoleate (Yu et al., 2019). Traditional SA industrial production process uses catalytic alkali decomposition of castor oil method (synthetic, non-extractive), castor oil acid to phenol as a diluent at 280–320°C with alkali cracking, after acidification, purification treatment to obtain SA (Yu et al., 2019). Due to the use of phenol and excess alkali for each ton of SA production, on average, about 30 t of difficult-to-manage phenol-containing salt wastewater, if not managed, will endanger human and animal safety due to land salinisation (Hang et al., 2013) (Figure 1).

Ricinoleic acid is the cleavage starting point for synthesizing 10-HDAA, followed by 10-H2DA. Under microwave radiation, ricinoleic acid was subjected to two alkali cleavages in a strongly alkaline medium to make the sodium salt of 10-HDAA, followed by acidification with sulfuric acid until the Congo Red test paper turned blue, standing, filtering, and drying to give a light-yellow solid, that is, 10-HDAA (Zhang & Gao, 2008). 10-HDAA is reacted with acetic anhydride to produce 10-acetoxy decanoic acid, which is subjected to α-bromination, followed by an elimination reaction to introduce a double bond, standing, filtering, and drying to obtain 10-H2DA (Li et al., 2007).

Studies have found that SA and 10-H2DA also have the potential to be added to food or pharmaceutical products, but the SA and 10-H2DA used, all of which are industrially produced, are not food-grade extracted. Several attempts were made to extract fatty acids from RJ (Geng et al., 2010; Liu et al., 2015). The extraction rate of 10-H2DA was as high as ~34%. Still, the amount of SA extracted was only 0.102%–0.179% of the raw material (Figure 2). Xu et al. (2009) compared five ethanol extraction processes for 10-H2DA and obtained 10-H2DA with a purity of 62.44% by one-time extraction under mild reaction conditions in a 6-step reaction. Although the study optimized the ethanol concentration, material-to-liquid ratio, extraction temperature, extraction time, and the number of extraction times, the maximum amount of product obtained from multiple extractions was not determined. In contrast, the SA extraction process presents a food safety risk due to using formic acid as a solvent. In addition, the failure rate of 0.064%–0.111% is also an enormous loss, but based on 5 g of raw material, SA was obtained at a higher rate than 10-H2DA. More environmentally friendly, safe, efficient, and recyclable food-grade SA and 10-H2DA extraction processes are still uncommon, especially food-grade extraction processes for 10-H2DA maximum amount obtained and high-quality SA.

2.2 | The metabolism of SA, 10-H2DA, and 10-HDAA

Fatty acids often experience two forms of oxidation: β-oxidation (leads to acetyl-CoA) and ω-oxidation (leads to the production of carboxyl). SA shares the same chain length as 10-HDAA and 10-H2DA but possesses different local functional groups (Figure 3). It hypothesized that all ingested 10-H2DA and 10-HDAA underwent ω-oxidation (Yamaga et al., 2019). Above all, the terminal $-CH_2OH$ group of 10-H2DA is oxidized to a –COOH group. 10-H2DA is then oxidized to 2-decenedioic acid, followed by further oxidation to azelaic acid. On the other hand, 10-HDAA is oxidized to SA and then oxidized to 3-hydroxy SA (3-HSA). These C9 dicarboxylic acids are then shortened by multiple β-oxidations to short-chain dicarboxylic acids and finally enter the tricarboxylic acid (TCA) cycle (Yamaga et al., 2019).

On one hand, SA is directly produced endogenously by C10 ω-oxidation (Chen et al., 2019). On the other hand, both SA and dodecanedioic acid are indirectly formed through the β-oxidation of long-chain dicarboxylic acids in organisms (Ranea-Robles et al., 2021). In turn, the corresponding fatty acids are ω-oxidized to produce the long-chain dicarboxylic acids on microsomal membranes

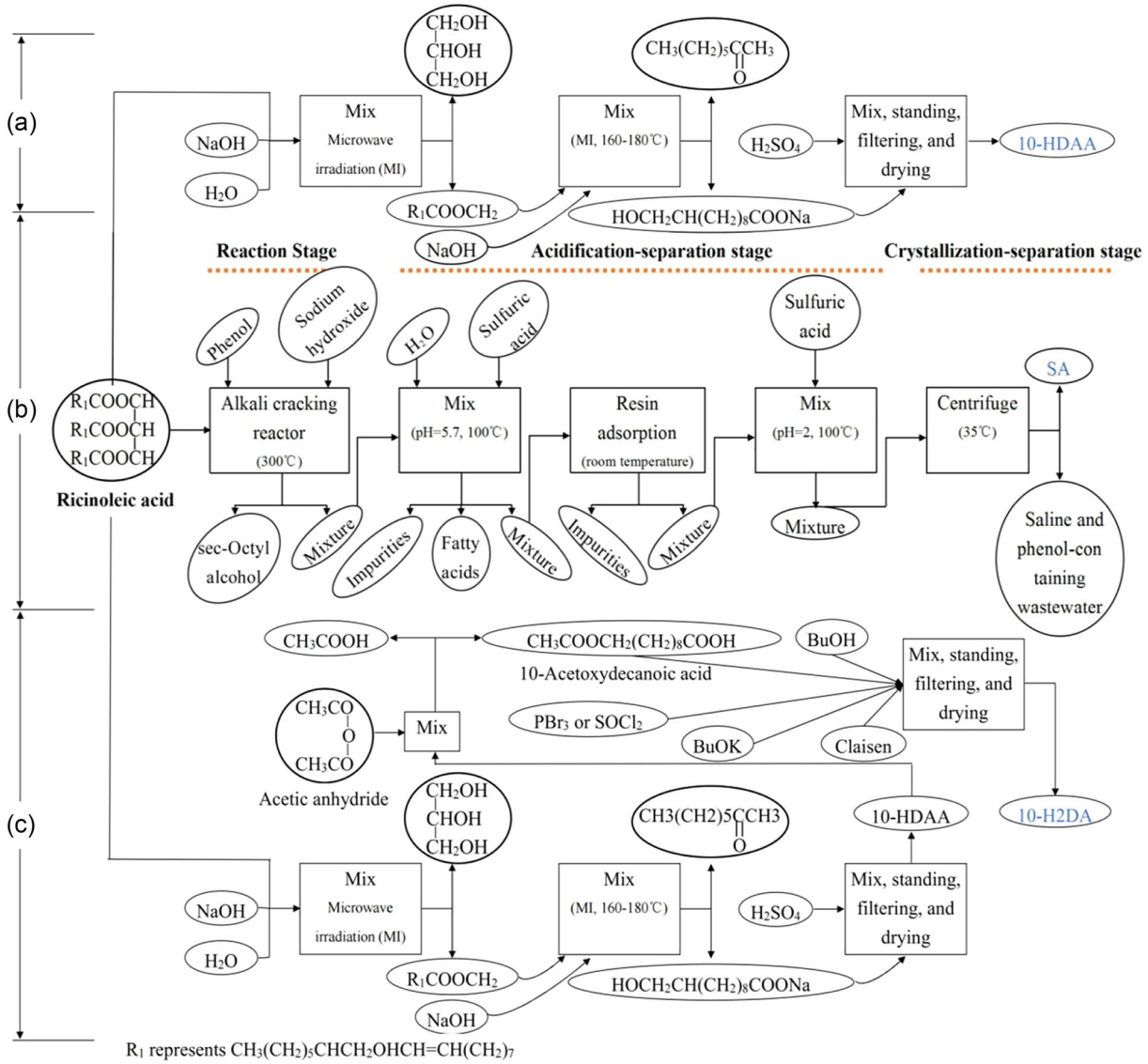

FIGURE 1 Typical industrial production process for (a) 10-hydroxydecanoic acid (10-HDAA), (b) sebacic acid (SA), and (c) trans-10-hydroxy-2-decanoic acid (10-H2DA).

or are ingested in a vegetable-rich diet (Chen et al., 2019). First, ω-oxidation has long-chain dicarboxylic acids. Then, β-oxidation produces SA (Figure 3). The catabolism of SA produces succinyl-CoA and acetyl-CoA (Figure 4) (Bharathi et al., 2020). However, a recent study by Sang et al. (2023) revealed that SA might overcome defects in mitochondrial TCA function in diabetic skeletal muscle, increasing gluconeogenesis and improving glucose clearance throughout the body. In a study by Iaconelli et al. (2010), the authors documented that dicarboxylic acid can be chain-shortened in mitochondria and peroxisomes to produce SA, which in turn becomes succinate. Succinic acid is a substrate of the TCA cycle, and its concentration may affect the concentration of oxaloacetate (a key metabolite) in this cycle. This acid contributes to the regulation of citrate synthesis, which leads to diminished ketogenesis by increasing acetyl-CoA shunting into the TCA cycle (Ito et al., 2021). In addition, SA oxidation may play a role in energy metabolism by gluconeogenesis (Liu et al., 2020). In a study by Ranea-Robles et al. (2021), after administration of adipic acid (a 6-carbon dicarboxylic acid) to ketotic rats, urinary excretion of succinate increased, along with a decrease in ketosis and an increase in blood glucose, SA and C6 may play the same role in this regard.

Although SA is not classified as a classical nutrient, it has been suggested as a potential substrate for glucose in people with Type II diabetes and severe illness. This suggestion is made because the body may require large amounts of energy under stressful conditions when glucose utilization is significantly impaired due to decreased

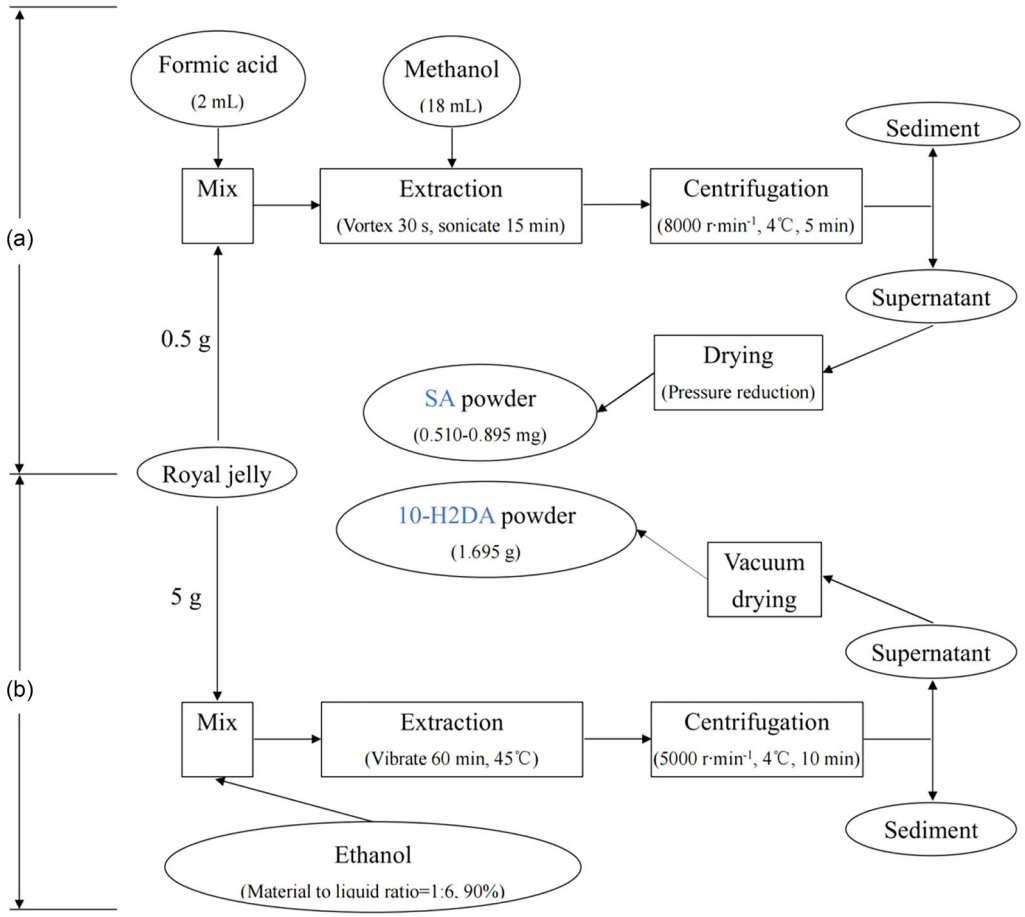

FIGURE 2 Typical extraction process of (a) sebacic acid (SA) and (b) trans-10-hydroxy-2-decanoic acid (10-H2DA) from food sources.

aerobic glycolysis and insulin resistance (Arruebo & Sebastian, 2020). In myoblasts (L6), SA dramatically stimulates glucose transporter4 expression and insulin-mediated glucose uptake, and its oxidation increases the concentration of medium-chain dicarboxylic acids (MCDAs), which can provide rapidly available energy (Iaconelli et al., 2010). The energy density of SA (6.64 kcal/g) is roughly between the known values of conventional substrates, such as carbohydrates (4 kcal/g), protein (4 kcal/g), and fat (9 kcal/g) (Malaisse et al., 2000). During the oxidation of 1 mol of SA, 61 ATP (445.3 kcal/mol) were produced, which is ~47% and ~160% of the energy provided by palmitic acid and glucose oxidation, respectively (Table 2). To our understanding, there are no reports on the energy density of 10-H2DA and 10-HDAA. The metabolic relationship (Figure 3) shows that 10-H2DA and 10-HDAA can be oxidized to produce SA, and the oxidation process is accompanied by energy release. Therefore, the oxidation of 1 mol of 10-H2DA and 10-HDAA may have more than 61 ATP, respectively.

2.3 | Mechanisms underlying the action of SA, 10-H2DA, and 10-HDAA

Overlapping in some of the pharmacological activities among substances from RJ is reported. The first evidence of the hypolipidemic effect of major RJ proteins at the cellular level by Zhang et al. (2021) showed that these proteins might help peptide medicines that treat hepatic metabolic disorders brought on by nonalcoholic fatty liver disease even more. In addition, the major RJ proteins are also reported to possess immunological modulation, neuroprotection, anti-ageing, anti-tumor, antimicrobial, hypotensive, cell growth promotion, and wound healing properties (Tian et al., 2018). RJ also contains additional beneficial substances, such as flavonoids (1.28 mg/g) and phenolics (23.3 mg/g) (Nabas et al., 2014). Phenolic compounds, which come in a variety of forms, are primarily accountable for the health functionalities, such as antioxidants, antibacterial, antiviral, anti-inflammatory, and cardiopro-

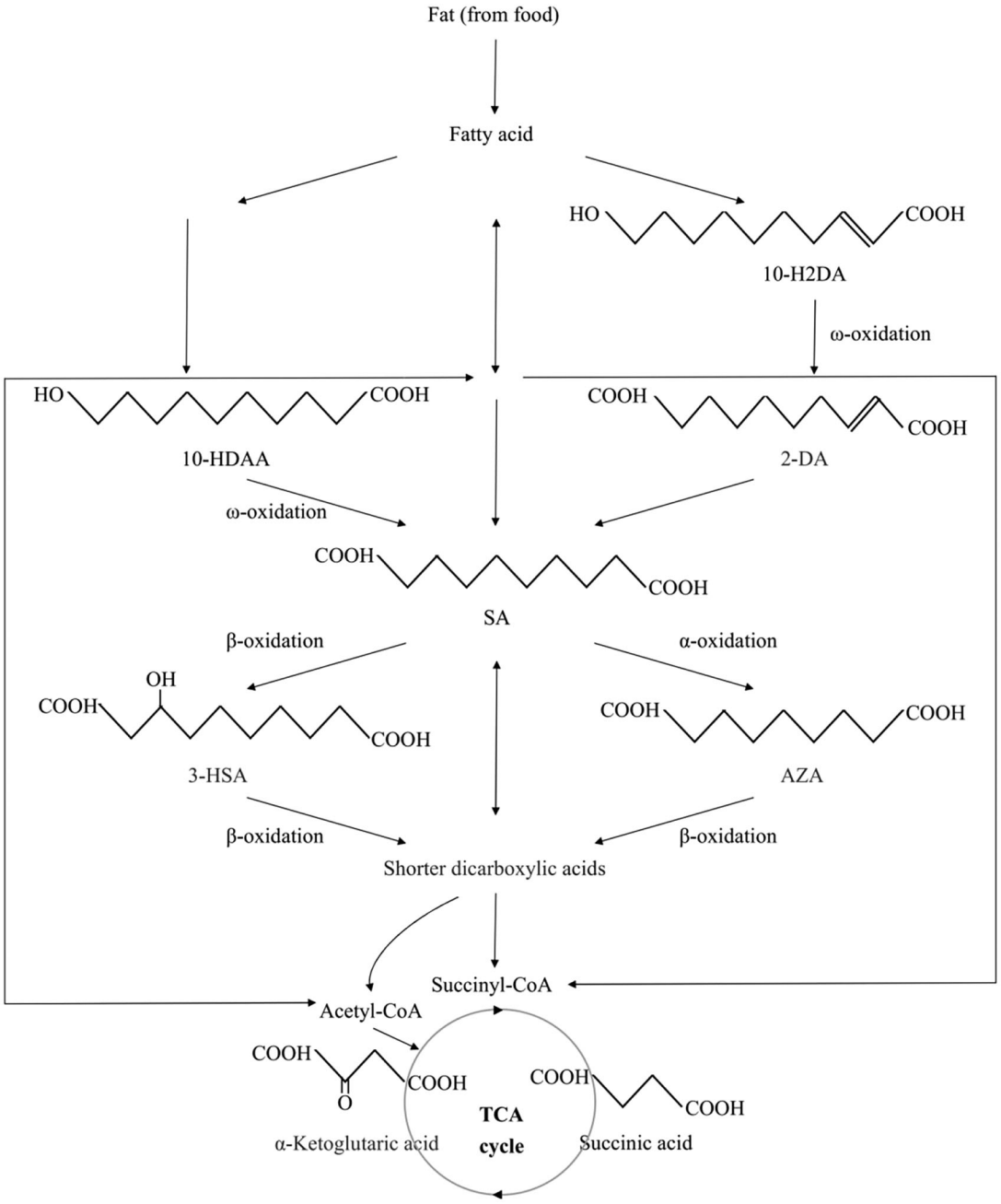

FIGURE 3 The metabolic relationship between sebacic acid (SA), 10-hydroxydecanoic acid (10-HDAA), and trans-10-hydroxy-2-decanoic acid (10-H2DA).

tective agents, of foods, as well as the ability to prevent enzymatic browning (Balkanska et al., 2017).

As was indicated above, there is mounting evidence that the components of RJ have synergistic effects. The peculiar functional fatty acid components of RJ are thought to be responsible for many of the biological characteristics of the substance, especially for 10-HDAA, SA, and 10-H2DA. They support a variety of biological actions of RJ, such as its anticancer, antibacterial, immunomodulatory, antioxidative, and anti-hypertensive properties, along with proteins (Chen et al., 2016). However, the compounds that mediate these effects remain unidentified. RJ extracts generally have more significant concentrations of functional components than the raw material, and they are used in scientific studies instead of the latter (Chen et al., 2016).

2.3.1 | Neurogenic and neurotrophic activity

One of the primary ways that 10-H2DA works as a treatment is by improving neurogenesis and neural functioning. It has been shown that in cultured brain

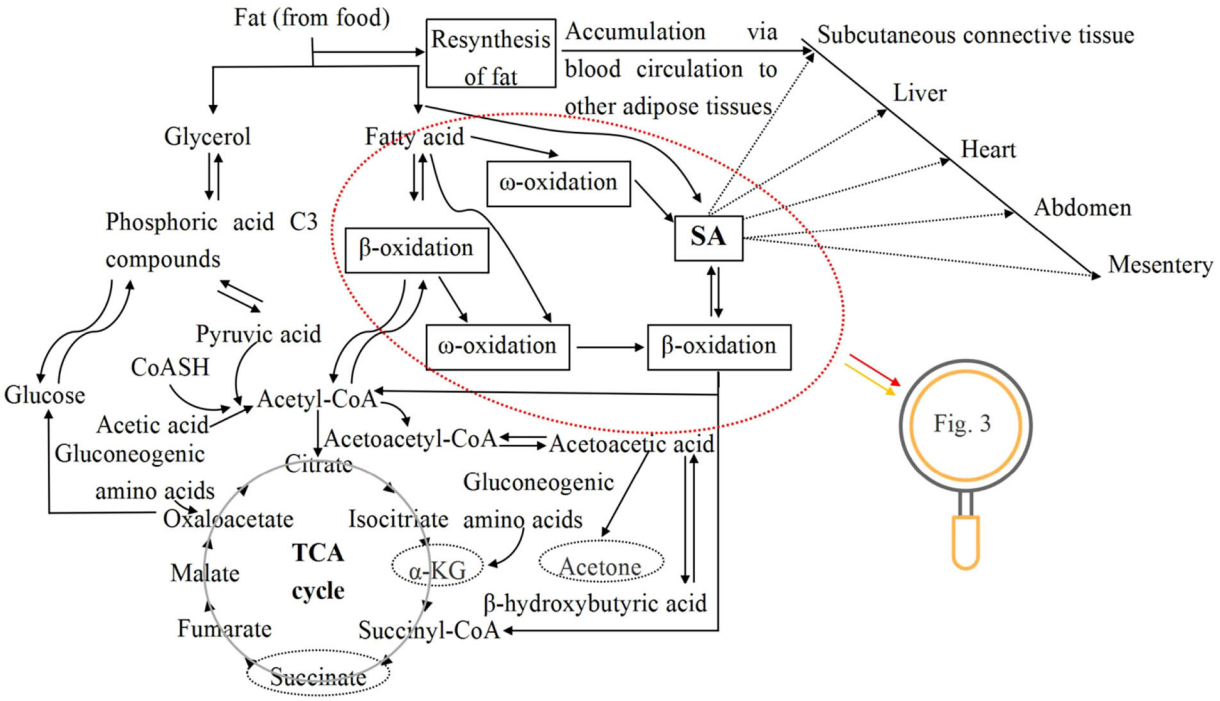

FIGURE 4 The proposed metabolic pathways of food-derived sebacic acid (SA) and endogenous SA. Fatty acids in food are *β*-oxidized and *ω*-oxidized to SA, which is then oxidized to water and carbon dioxide via acetyl-CoA and succinyl-CoA. In addition, succinyl-CoA can also be used as a starting point for the gluconeogenesis pathway. Refer to Figure 3 for more detailed information about the red dotted box.

TABLE 2 Energy metabolism of different substrates: sebacic acid, glucose, and palmitate.

	Reaction	ATP
Sebacic acid	*β*-Oxidation	61
	SA ⇨ 3 Acetyl-CoA ⇨ 6 CO2 + 3 FADH2 + 9 NADH + 3 GTP° + 6 H+ + 3 CoA	
	SA ⇨ Succinyl-CoA ⇨ ⇨ ⇨ 2 CO2 + FADH2 + 3 NADH + GTP° + 2 H+ + CoA	
	Gluconeogenesis	1
	Succinyl-CoA ⇔ … ⇔ glucose + Pi	
Glucose	Glucose complete oxidation	38
	$6\ O_2 + C_6H_{12}O_6 \Rightarrow 6\ CO_2 + 6\ H_2O$	
Palmitate	Palmitate complete oxidation	131
	Palmitoyl CoA ⇨ 8 acetyl CoA ⇨ TCA cycle ⇨ …	

Abbreviation: TCA, tricarboxylic acid.

stem/progenitor cells, 10-H2DA enhances neurogenesis while decreasing glial production. Although the precise mechanism at play is unclear, the authors proposed that 10-H2DA replicates the effects of brain-derived neurotrophic factor (BDNF) (Hattori et al., 2007). Neurons exposed to 10-H2DA became larger and formed more connections with other neurons (Weiser et al., 2017). In neurons subjected to glutamate and hypoxia challenges, which serve as models of age-related neurodegeneration and stroke, 10-H2DA also enhanced appropriately polarized mitochondria and reduced cellular death compared to untreated controls (Weiser et al., 2017). At present, it is speculated that the effects of BDNF are partially mimicked by 10-H2DA, and the events that were subsequently brought on by glial cell line-derived neurotrophic factor (GDNF) were associated with increased expression of neurofilament H (Ali & Kunugi, 2021).

Because of their comparable structures, it is anticipated that SA, 10-H2DA, and 10-HDAA may show similar effects. The neurotrophin-like effect of 10-H2DA and its derivatives is thought to be responsible for neurogenesis, neurite outgrowth-promoting activity, synapse

formation-promoting activity, and neuroprotective properties of neurons. This effect is caused by the phosphorylation of extracellular signal-regulated kinase 1 or 2 (ERK1/2), mitogen-activated protein kinase (MAPK), and cAMP response element-binding protein (CREB) in neurons (Kunugi & Mohammed Ali, 2019; Takahashi et al., 2012).

2.3.2 | Estrogen-like activity

RJ possesses estrogenic properties both in vitro and in vivo, as demonstrated by Mishima et al. (2005), whereby certain compounds in RJ can interact with estrogen receptors. The study further revealed that the expression of estrogenic actions requires 10-H2DA. In a later study by Moutsatsou et al. (2010), the authors identified the estrogenic properties of several lipids in RJ, which include MCFAs such as 10-H2DA, 10-HDAA, and SA. These compounds were discovered to influence estrogen receptors and modulate the activity of ERα and ERβ, which in turn mediate estrogen signaling. This impact will probably add to the neurogenic effects of these fatty acids because estrogen can control gene expression linked to brain function, body composition, and cell proliferation (Moutsatsou et al., 2010). In this sense, these MCFAs stimulate the estrogen-sensitive breast cancer cell line MCF-7 cell proliferation and transcription that is reliant on the estrogen receptor (ERα and ERβ) and the estrogen-responsive element (Suzuki et al., 2008). Additionally, the authors demonstrated how these lipids competitively inhibited the binding of 17β-estradiol to the human estrogen receptor β (but not the estrogen receptor α).

In the absence of 17β-estradiol, these MCFAs exhibited mild agonistic activity in MCF-7 cells expressing the estrogen receptor β (but not α). On the other hand, these MCFAs were agonistic in HeLa cells that expressed the estrogen receptor α (but not β). However, in cells expressing estrogen receptors α and β, these MCFAs counteracted the transactivation of the estrogen-responsive element caused by 17β-estradiol. It was discovered that 10-H2DA changed the recruitment of co-activators to estrogen receptor α triggered by 17β-estradiol. They hypothesized that these MCFAs cause a conformational change in estrogen receptors, which modulates the recruitment of estrogen receptors and co-activators to the target genes, even though 10-H2DA (but not the other lipids) is only weakly bound to the ligand-binding domains of estrogen receptors α and β (Moutsatsou et al., 2010).

2.3.3 | Antioxidant activity

One possible mechanism of action for RJ lipids and their derivatives is enhancing antioxidant capacity and preventing oxidative stress. Through enrichment of acetylated histone H3 and H4 in the proximal promoter region of extracellular superoxide dismutase (ECSOD), 4-hydroperoxy-2-decenoic acid ethyl ester (HPO-DAEE), 10-H2DA, and two other primary fatty acids found in RJ (10-HDAA and SA) stimulated the expression of ECSOD in THP-1 cells (Ali & Hendawy, 2019; Ali & Kunugi, 2021). However, only HPO-DAEE activated the phosphorylation of ERK. Notably, there is disagreement over data about RJ fatty acid antioxidant properties in the central nervous system. In human neuroblastoma SHSY5Y cell cultures, 10-H2DA, 10-HDAA, and SA could not prevent 6-OHDA-induced cellular death (Ali & Hendawy, 2019). In addition, astrocytes were not affected by 10-H2DA (300 mM). However, it did cause an abrupt and significant decrease in the mitochondrial electrical potential and a corresponding decrease in the NAD(P)H signal. Intracellular ATP levels remained constant despite the respiratory chain being blocked because of a compensatory mechanism that increased lactate production by 49.6% and stimulated glycolysis (Ali & Hendawy, 2019).

2.3.4 | Anti-inflammatory activity

10-H2DA, 10-HDAA, and SA from RJ were found to be correlated with the anti-inflammatory properties of the RJ. These fatty acids prevented nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) expression by phosphorylating ERK1/2 and JNK1/2 and mediating JNK signaling pathways, respectively (Uthaibutra et al., 2023). Rather than increasing the expression of anti-inflammatory mediators, 10-HDAA inhibited pro-inflammatory mediators (You et al., 2020). By lowering iNOS expression, 10-HDAA inhibited the LPS-induced increase in NO levels in BV-2 cells. Meanwhile, 10-HDAA may have an inhibitory effect on NLRP3 inflammatory vesicles, which reduced reactive oxygen species levels in BV-2 and N9 cells in a dose-dependent manner. It may also reduce inflammation by increasing the expression of TREM2 in microglial cells. Notably, You et al. (2020) demonstrated 10-HDAA's potent anti-inflammatory effects in microglial cells for the first time and pinpointed a brand-new mode of action. Reducing inflammation in BV-2 cells by 10-HDAA could potentially involve the NF-κB pathway

(You et al., 2020). Similarly, 10-H2DA modulated cellular responses to LPS, IFN-β, and IFN-γ challenge by suppressing IFN-β-induced NF-κB signaling and IFN-γ-mediated activation of interferon regulatory factor−8. This resulted in an inhibition of NO and tumor necrosis factor-alpha (TNF-α) production. In contrast, LPS-stimulated IFN-β generation, IFN regulatory factor-1 induction, and IFN-stimulated response element activation—all necessary for nitric oxide synthase (NOS) induction—were unaffected by 10-H2DA (Ali & Hendawy, 2019). However, contradictory information regarding the molecular processes behind 10-H2DA's anti-inflammatory actions is available. Significant inflammatory mediators, NO, and interleukin-10 were decreased in a dose-dependent manner by 10-H2DA, 10-HDAA, and SA; among these, TNF-α production in LPS-challenged RAW264.7 macrophages was only suppressed by SA. The regulation of proteins involved in the NF-κB and MAPK signaling pathways mediated these effects (Ali & Hendawy, 2019).

2.3.5 | Anti-tumor activity

Epigenetic mechanisms play a significant role in tumorigenesis, tumor progression, and the development of various types of cancer (Cheng et al., 2018). It has been known that enzymes, including DNA methyltransferases, histone acetylases and deacetylases, and histone methyltransferases and demethylases, are responsible for maintaining an epigenetic state. There are nutritional factors that can target these enzymes (Cheng et al., 2018). 10-H2DA can inhibit histone deacetylase (HDAC) activity without changing DNA methylation (Shirakawa et al., 2020). Nonetheless, it is plausible that RJ contains a substance that targets DNA methyltransferases at particular loci with selectivity, which would work in concert with 10-H2DA (Spannhoff et al., 2011). One study has indicated that 9- and 10-carbon straight-chain monocarboxylic acids, whether saturated or unsaturated, are mostly linked to the targeted activity of 10-H2DA (Townsend et al., 1961). It may be possible for 10-HDAA to help 10-H2DA target DNA methyltransferases. Makino et al. (2016) found that SA, 10-H2DA, and 10-HDAA could directly inhibit the HDAC catalytic domain, but whether SA and 10-HDAA could alter DNA methylation remains unreported.

2.3.6 | Glucose regulation activity

10-H2DA and SA help both human and animal models of diabetes by reducing insulin resistance and hyperglycemia (Inoue et al., 2022). SA dramatically lowers glucose rate of appearance and post-meal glucose circulating levels in both insulin-resistant Type II diabetes patients and healthy individuals (Iaconelli et al., 2010). SA's ability to diminish endogenous glucose output after a meal may be due to its ability to produce succinic acid through mitochondrial β-oxidation, which enters the mitochondrial TCA cycle. Type II diabetic people have been shown to have decreased in vivo function of mitochondria in their skeletal muscle both at rest and throughout the recovery period following exercise (Huang et al., 2023). A decreased flux of the mitochondrial TCA cycle appears to be the cause of this compromised mitochondrial oxidative capacity (Iaconelli et al., 2010). As skeletal muscle tissue is the primary source of glucose absorption, SA may be able to improve whole-body glucose clearance by supplying succinic acid, which would compensate for the impaired function of mitochondrial TCA in diabetes-related skeletal muscles (Iaconelli et al., 2010).

Furthermore, the level of blood SA shows a negative correlation with body weight, fat mass, and waist. Tataranni et al. (1992) suggested that the half-life of sebacate is longest in the liver and adipose tissue, sites of likely transformation. It is hypothesized that MCFAs are transported through the portal vein to the mitochondria of hepatocytes for oxidation, producing large amounts of SA and glycerol. SA in the liver may reduce weight gain and fat accumulation by inhibiting adipogenesis and promoting lipolysis. At the same time, other SA is sent to other tissues via blood circulation and inhibits their fat deposition. Nevertheless, the effect of SA on fat metabolism has never been studied, not as a metabolite but in addition to available carbohydrates.

In non-inflammatory conditions, 10-H2DA (3 μM) had an insulin-like growth factor 1 (IGF-1)-raising effect (Ali & Kunugi, 2021). In contrast, after LPS exposure, astrocytes' mRNA expression of IGF-1 was decreased by 10-H2DA. Under normal circumstances, astrocytic glucose metabolism is believed to be improved by insulin sensitivity, which is increased by downregulating IGF-1 (Ali & Kunugi, 2021). Over the past 20 years, research has demonstrated that nonesterified MCFAs can directly affect biological processes like metabolism and immunological responses by interacting with free fatty acid receptors, such as GPR40 and GPR84. MCFAs have the potential to activate GPR40, which could influence the secretion of insulin from pancreatic β cells (Kokotou et al., 2020).

2.3.7 | Antibacterial activity

Fatty acids exhibited their antimicrobial mechanisms by suppressing cellular energy production, inhibiting DNA/RNA replication, disrupting enzyme activity, causing disorders in nutrient uptake, generating peroxidation

and autooxidation degradation products, and disrupting the cytoplasmic membrane (Alkhaibari & Alanazi, 2022). On the one hand, potent bactericidal activity is observed with SA, 10-H2DA, and 10-HDAA in mildly acidic conditions. However, this activity significantly decreases upon neutralization (Isidorow et al., 2018). On the other hand, NO generation was stimulated by 10-H2DA, 10-HDAA, and SA (Hanai et al., 2023). This gas is considered an appealing bactericidal agent because it can eliminate germs, break up biofilms, and accelerate the healing of wounds infected with bacteria while preventing resistance (Hall et al., 2019). In addition, 10-H2DA, 10-HDAA, and SA specifically induced parasite caspase-3 activation without affecting human HEK239T normal cells. Caspase-3 is a critical mediator that mainly triggers death proteases and successively contributes to cell death (Hanai et al., 2023). It is important to note that the specific mechanisms can vary depending on the context, cell type, and concentration of these acids. The multifaceted nature of their actions makes them potential candidates for various applications, from health promotion to disease prevention.

2.4 | Potential nutraceutical industry applications of SA, 10-H2DA, and 10-HDAA

The nutritional sector is investigating SA, 10-HDAA, and 10-H2DA without distinct divisions between functional foods and dietary supplements. However, 10-H2DA in RJ is more heavily studied in food nutrition than SA and 10-HDAA. It offers sex-dependent advantages for muscle mass, adiposity, and bone density (Althobaiti, 2022).

2.4.1 | Stress relief and memory improvement

According to the research by Weiser et al. (2017), oral intake of 10-H2DA (12–60 mg/kg/day) for ≥3.5 months, equivalent to RJ (0.6–10 g/kg/day), promotes neuron growth, shields them from harm, and lessens anxiety-like behavior. Pro-growth signaling appears to be how 10-H2DA works in the brain (Weiser et al., 2017). In the hippocampus, mice given 1% RJ (about 1.5 g RJ/kg; around 3 mg 10-H2DA/kg) for 10 days showed elevated mRNA for neurofilament H and GDNF. Furthermore, it was hypothesized that 10-H2DA would trigger neurite outgrowth by activating collagen synthesis and integrin signaling; however, this claim was based on 10-H2DA effects in fibroblasts rather than neurons. Given that oestradiol has the same effect, the discovery that 10-H2DA promotes collagen formation in fibroblasts raises the possibility of a connection with the oestradiol system. Additionally, dose-dependent mood enhancement, protection against stress-related neuronal death, increased neurite outgrowth, and non-genomic ERK activation are all provided by oestradiol (Weiser et al., 2017).

The muscle and adipose tissue findings indicate once more that 10-H2DA and oestradiol share signaling characteristics. In other words, these broad effects of 10-H2DA seem in line with the relationships that have been found in human males between oestradiol, muscle protection, and loss of lean mass, and in females between oestradiol, adiposity, and glucose utilization (Weiser et al., 2017). In part, 10-H2DA has excellent potential for muscle-sculpting, weight loss, and anxiety-relieving food formulations, for example, fudge and pop beads (Cornara et al., 2017).

Cytokines, such as TNF-α, can influence the proliferation of human neural progenitor cells (Hagman et al., 2019). However, any *cis*-elements in the promoter region of the TNF-α gene are responsive to NF-κB, NFAT, and CREB. Although aspirin (a nonsteroidal anti-inflammatory drug) and 10-HDAA alone were ineffective in treating LPS-induced memory impairment, their combined therapy had positive effects. 10-HDAA first inhibited the NF-κB pathway's activity before focusing on Ptgs-1/2, aspirin's well-known target. Pro-inflammatory mediator levels were lowered, and the combination treatment synergistically reduced glial cell over-activation. Additionally, 10-HDAA reduced the adverse effects of aspirin on dysbiosis of the microbiota and gastrointestinal injury (You et al., 2022).

Besides 10-HDAA, clinical trials have found that rats treated with RJ and 10-H2DA enhanced their neurotransmitters and antioxidant biomarkers. Interestingly, 10-H2DA (3 μM in vitro) and RJ (300 mg RJ/kg in vivo) also activated the central nervous system, as evidenced by decreased oxidative stress and apoptosis in brain tissue (Mohamed et al., 2015). Because it was shown that 10-H2DA might support the development of neurons in addition to its anti-oxidative capabilities, the 10-H2DA-induced decrease in IGF-1 in activated astrocytes may increase mitochondrial capacity. The altered mitochondrial metabolism results in cellular stress linked to increased interleukin 6 (IL-6) production. IL-6 may then trigger the release of other cytokines, extending the lifespan of these cells and the neurons surrounding them. It is hypothesized that 10-H2DA might be a factor that accounted for these alterations (Ali & Kunugi, 2021; Mohamed et al., 2015). Hence, it is worth mentioning that, according to the researchers, RJ's antioxidant capabilities are due to compounds like 10-H2DA and free amino acids (Uthaibutra et al., 2023).

2.4.2 | Bone health

Sex hormones may interfere with the 10-H2DA effect on body composition. Numerous actions of estrogen are mediated through the two nuclear ERs: ERα and ERβ. All skeletal cell categories, including progenitor cells, osteocytes, osteoclasts, and osteoblasts, have been shown to harbor both ERs (Hanai et al., 2023). The estrogen receptor system may have a role in the effects of RJ and 10-H2DA on cells connected to bone, and larger dosages may not necessarily translate into better results. It is interesting to note that 10-H2DA alone (1–10 nM) enhanced osteoblast mineralization to a level comparable to that of oestradiol (1 nM). By stimulating bone-cell proliferation, collagen synthesis, and mineralization through pathways connected to estrogen receptors, 10-H2DA, the active ingredient in RJ, enhances bone density (Weiser et al., 2017). Further, Tsuchiya et al. (2020) have shown that 10-H2DA from RJ inhibits NF-κB signaling through its free fatty acid receptor 4 to reduce osteoclastogenesis. Given that RJ is among the most widely consumed foods that promote health, RJ supplementation, along with the administration of 10-H2DA, may be employed as a therapeutic method to treat a variety of metabolic bone illnesses, including osteoporosis.

However, Tsuchiya et al. (2020) hypothesized that RJ contains additional anti-osteoclastogenic molecule(s) in addition to 10-H2DA because osteoclast genesis was prevented, albeit to a lesser degree, at concentrations of 10-H2DA equal to those reported in RJ (1.54%). The applications of SA and 10-HDAA in increasing bone density have been reported less frequently. As they also possess a mechanism of action that mediates estrogen signaling, they have greater potential for use in the development of products to increase bone density.

2.4.3 | Liver health

10-H2DA has been discovered that this fatty acid reduces hyperlipidaemia in a rat model. It has hepatoprotective effects on the liver of mice with acute alcoholic liver injury. The hepatoprotective effects reported were linked to the increment in the liver index, reduction in the levels of several parameters (total cholesterol, triglyceride, and very-low-density and low-density lipoprotein cholesterols) in the serum, and reduction in the serum activities of aspartate aminotransferase and glutamic pyruvic transaminase. It is also effective in reducing the occurrence of fatty vacuoles and aqueous degeneration in liver tissue and maintaining the stability of the standard ecophysiological structure of liver cells (Niu et al., 2020). Moreover, 10-H2DA can promote the secretion of alcohol dehydrogenase and acetaldehyde dehydrogenase, increase glutathione content and total nitric oxide synthase, superoxide dismutase, glutathione peroxidase, and inducible nitric oxide synthase activity, and reduce the range of malonaldehyde and monoamine oxidase activity (Niu et al., 2020). The amount of 2.5–5.0 mM 10-H2DA used by Chen et al. (2016), ~37 g of raw RJ, suggests a secondary mechanism of action for anti-inflammatory pathways. If taken for a long time, 10-H2DA can also effectively enhance the antioxidant capacity of the liver (Niu et al., 2020). For chronic excessive drinkers, 10-H2DA is expected to maintain their liver's health, improve fat metabolism, and lower blood lipids (Kobayashi et al., 2023).

2.4.4 | Immunity improvement

10-H2DA, SA, and 10-HDAA exhibit anti-inflammatory actions by controlling many proteins implicated in nuclear factor kappa-B and MAPK signaling (Chen et al., 2016). Several reports have shown the immunomodulatory effects of 10-H2DA, including a reduction in the growth of T cells, suppression of the formation of interleukin-12 by spleen dendritic cells, and shut obstruction of LPS- and IFN-β-induced nitric oxide generation in macrophages (Chen et al., 2016; Shahla et al., 2021). Long life expectancy and enhanced immunity are inextricably linked. The life-extending effects of RJ and 10-H2DA are associated with downstream processes of dietary restriction of signaling, particularly 10-H2DA (Vieira et al., 2021).

Notably, a study by Filipič et al. (2019) found that both RJ (0.1 g/10 mL) and 10-H2DA (100.0 μmol/L) inhibited the growth of human colorectal adenocarcinoma (CaCo-2) cells, downregulated oxidative stress, and increased concentrations of lipid peroxidation markers. The regulation of oxidative stress and activation of apoptosis are two potential anticancer mechanisms of RJ. Similar effects were observed in 10-H2DA. The findings from the study concluded that the antiproliferative effects of RJ and 10-H2DA on the tested cells were related to their impact on the prooxidant–antioxidant balance and the induction of apoptosis and cytotoxicity. In this direction, 10-H2DA has the potential to be manufactured as an anticancer product. Moreover, restriction on the HDAC activity by 10-H2DA was hypothesized to increase the expression of ECSOD release by leukemia human myeloid leukemia mononuclear-1 cells, leading to the suggestion of 10-H2DA as a prospective treatment against atherosclerosis (Makino et al., 2016).

On the contrary, Uthaibutra et al. (2023) noted that the presence of 10-HDAA, free amino acids, and phenolic compounds were the leading causes of RJ's antioxidant

characteristics. RJ's ability to prolong life may be due to its anti-inflammatory and antioxidant characteristics, which can also stop the development of some crippling metabolic illnesses (Bianco, 2022). According to a study, 10-HDAA (0.5–2.0 mM) separated from RJ inhibits matrix metallopeptidase-1 and matrix metallopeptidase-3 activity in synovial fibroblasts, which mediate joint degradation in rheumatoid arthritis, possibly through inhibiting the p38 and c-Jun N-terminal kinase-activator protein-1 signaling pathways (Yang et al., 2010). Meanwhile, an in vitro investigation suggested that 10-HDAA may be a secure rheumatoid arthritis treatment for preventing joint destruction (You et al., 2020). Thus, 10-HDAA can be used as an alternative to nonsteroidal anti-inflammatory drugs in treating inflammation and reducing gastrointestinal and hepatic side effects. It increases the expressions of interleukin-6, tumor necrosis factor, monocyte chemoattractant protein-1, and pro-inflammatory mediators. However, the anti-inflammatory mediator interleukin-10 expression remains unchanged (You et al., 2020).

The development of SA, 10-HDAA, and 10-H2DA for healthcare products is mainly based on the direction of RJ applications. RJ promotes skin healing following wounds, whereas major RJ protein 3 inhibits the pro-inflammatory cytokine synthesis and activates keratinocytes for healing wounds (Minegaki et al., 2020). RJ has hormone-like properties that reduce inflammation, whereas 10-H2DA controls collagen secretion to promote wound healing and is suitable for developing a wound dressing containing 10-H2DA (Alvarez et al., 2022). On the other hand, the reduction of lipopolysaccharide-induced nuclear factor-B activation seen in the mouse macrophage cell line RAW264 was discovered to be a mechanism connected with the anti-inflammatory action of 10-H2DA in a study on RJ for the treatment of gastrointestinal illnesses (Chen et al., 2016). Multiple proteins involved in the MAPK and NF-κB signaling pathways were controlled by 10-H2DA (1–5 mM) in lipopolysaccharide-stimulated RAW 264.7 macrophages (Chen et al., 2016). Thus, 10-H2DA also has excellent potential for creating products that treat or prevent stomach ulcers.

2.4.5 | Blood glucose and lipids regulation

Eight years ago, SA was proposed as an alternative energy substrate for total parenteral nutrition (Liu et al., 2021). Yamaga et al. (2019) suggested that the body's metabolism of fatty acids, especially MCFAs, is enhanced in protease-treated RJ, and the elevated SA content may benefit blood glucose regulation. The intake of SA (23 g) as part of an in-combination diet has been demonstrated to reduce postprandial glucose and hepatic glucose production in patients with Type II diabetes without stimulating insulin secretion (Iaconelli et al., 2010). Nevertheless, clinical studies of oral SA for treating Type II diabetes are still relatively few and are mainly focused on animal studies. Besides, glucose metabolism is closely linked to lipid metabolism, and there are also few studies on the effects of SA on lipid metabolism in the clinical setting.

It has been claimed that consuming RJ can lower serum cholesterol levels. In a related mechanistic study, SA (0.5–1.5 mM) significantly downregulates angiopoietin-like protein 8 expression in human hepatoma HepG2 cells by reducing HNF4α protein. Namely, SA is one of the main functional components of RJ for lowering blood lipids (Inoue et al., 2022). Indeed, Nestlé Product Technical Assistance Ltd. applied for and was granted a patent in 2009 for adding four MCDAs, including SA, to coffee. The patent describes the combination (mainly SA) used to treat or prevent hyperglycemia (Mingrone & Metz, 2009). To the best of our understanding, research on SA application in foods is scarce.

The translocation of glucose transporter4 to the plasma membrane and the activation of AMP-activated protein kinase, which involves estrogen receptors, 10-H2DA increase insulin-independent muscle glucose absorption, according to research done in vitro on rat L6 myotubes and in vivo on mice (Ibrahim & Kosba, 2018). In this direction, 10-H2DA is expected to be used in the development of products for controlling blood glucose.

3 | CONCLUSIONS

This review synthesizes data from various studies to establish the potential biological activity and physicochemical properties of three active compounds, SA, 10-HDAA, and 10-H2DA, as functional and health-promoting foods. These compounds are envisioned as preventive measures against relevant diseases while enhancing product quality and consumer perception of use. Based on the literature review from the studies conducted in recent years, we have identified the great potential for the application of SA, 10-HDAA, and 10-H2DA in the nutraceutical industry. However, additional application research is needed to ascertain the feasibility of SA, 10-HDAA, and 10-H2DA in concrete implementation.

From the advantaged discovery of MCDA over traditional lipid substrates (long and medium glycerides), researchers have shown great interest in the immediate availability exhibited by these compounds, speculating that many of its applications extend beyond chemical materials. Although SA, 10-H2DA, and 10-HDAA are mainly of industrial origin, new research developments have been made in nutraceutical applications in recent

years. We expect to see more research into the application of SA, 10-H2DA, and 10-HDAA in various areas beyond traditional industrial manufacturing, disease prevention and treatment, and addition to food products.

AUTHOR CONTRIBUTIONS

Zhengrui Liao: Writing—review and editing; writing—original draft; conceptualization. **Mohammad Alrosan**: Investigation. **Muhammad H. Alu'datt**: Formal analysis. **Thuan-Chew Tan**: Writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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