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Contribution of Lipids in Honeybee (*Apis mellifera*) Royal Jelly to Health

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ABSTRACT Honeybee (*Apis mellifera*) royal jelly (RJ) has a long history in human medicine because of its health-protecting properties. To develop a fundamental and comprehensive understanding of lipids in RJ, this article reviews the available literature on lipid compounds identified from RJ extracts and *in vitro* pharmacological effects of 10-hydroxy-2-decenoic acid in RJ and other closely related compounds, some of which are also identified as lipid compounds in RJ. Overall, the lipids in RJ are composed of mostly (aliphatic) fatty acids, almost all of which are present as free fatty acids and scarcely any as esters. Most fatty acids in RJ are medium-chain fatty acids, whether hydroxylated in terminal and/or internal positions, terminated with mono- or dicarboxylic acid groups, and saturated or monounsaturated at the 2-position. Besides these fatty acids, lipids in RJ contain sterols in minor amounts. Lipids in RJ are useful as preventive and supportive medicines with functionalities that include potential inhibitors of cancer growth, immune system modulators, alternative therapies for menopause, skin-aging protectors, neurogenesis inducers, and more. Taken together, the evidence suggests that health-protecting properties of RJ can be, in part, ascribed to actions of lipids in RJ.

KEY WORDS: • *fatty acid* • *health functional food* • *lipids* • *royal jelly*

INTRODUCTION

HONEYBEES ARE ADAPTED for feeding primarily on nectar and pollen from insect-pollinated flowering plants, from which they produce royal jelly (RJ). RJ, called honeybee's milk by some, is secreted from hypopharyngeal and mandibular glands of 3- to 12-day-old workers (nurses) and fed to the queen bee all through her life and to early-instar larvae in worker and in drone cells just for the first three days. Carbohydrates, proteins, and lipids are the major nutritional components of RJ, and the first two in the gland secretion are assumed to be synthesized by the hypopharyngeal glands,[1–4] and the last synthesized by the mandibular glands.[5,6] Similar to milk from other animals, RJ is also rich in lipids (including fatty acids and sterols), accounting for 4%–8% of the fresh matter or 15%–30% of the lyophilized product.[7] The diverse nature of lipids in RJ, whether in structure or in species, has been detected in many tests.[8–10]

RJ has been used as a human medicine for its health-protecting properties. 10-hydroxy-2-decenoic acid (10-HDA), considered as a characteristic constituent of lipids in RJ and applied as an index for estimating quality of RJ,[11,12] has been shown to possess a variety of *in vitro* pharmacological effects in studies, such as antitumor,[13,14] immunomodulatory,[15–18] estrogen-like,[11] collagen production-promoting,[19] and neurogenesis-promoting[20] effects. However, the full spectrum of lipids in RJ has not been adequately described, and their characteristics and bioactivities remain largely unknown.

To develop a fundamental and comprehensive understanding of lipids in RJ, this article reviews available literature on lipid compounds identified in lipid extracts from RJ and *in vitro* pharmacological effects of 10-HDA in RJ and other closely related compounds, some of which are also identified as lipid compounds in RJ.

DISCUSSION

Compositional properties of lipids in RJ

A majority of fatty acids. The majority of lipids in RJ are fatty acids, mostly in free form and rarely in esters. At least ninety-four free fatty acids have been detected in lipid extracts from RJ (Table 1).[7,11,20–33] According to the current classification scheme that organizes fatty acids and conjugates into seventeen well-defined subclasses of fatty acyls,[34] these acids in RJ may be classified according to their molecular structures into six subclasses as follows: (1) straight-chain fatty acids, such as pentanoic acid; (2) unsaturated fatty acids, such as 2-decenoic acid; (3) hydroxy fatty acids, such as 10-hydroxydecanoic acid (10-HDAA); (4) oxo-fatty acids, such as 11-oxo dodecanoic acid; (5) dicarboxylic

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Table 1. Organic Acids Detected in Lipid Extracts from Royal Jelly

IUPAC (with or without other trivial) name and molecular size	*Relative amount*[7] *Min*	*Max*
I. Free (aliphatic) fatty acids		
Acetic (ethanoic)[7]	nr	nr
2-Hydroxyethanoic (glycolic)[7]	Trace	0.03
Main chain length of 2 carbon atoms		
2-Hydroxypropanoic (lactic)[7]	0.01	0.1
2,3-Dihydroxypropanoic (glyceric)[7]	Trace	0.02
Main chain length of 3 carbon atoms		
Butanoic (butyric)[7]	nr	nr
2-Methylbutanoic (2-methylbutyric)[21,22]	/	/
3-Methylbutanoic (delphinic)[21,22]	/	/
(1,4-)Butanedioic (succinic)[7]	0.01	0.1
2-Hydroxybutanedioic (malic)[7]	Trace	0.03
Main chain length of 4 carbon atoms		
Pentanoic (valeric)[22]	/	/
3-Methylpentanoic (3-methylvaleric)[21,23]	/	/
2-Hydroxy-4-methylpentanoic (2-hydroxy-4-methylvaleric)[22]	/	/
3-Hydroxy-3-methylpentane(-1,5-)dioic (3-methyl-3-hydroxyglutaric)[7]	Trace	0.03
Main chain length of 5 carbon atoms		
Hexanoic (caproic or n-caproic)[21,22]	/	/
2-Ethylhexanoic (2-butylbutanoic)[21]	/	/
2-Hydroxyhexanoic (2-hydroxycaproic)[21,22]	/	/
Hexane(-1,6-)dioic (adipic)[7,24]	–	–
2-Hexenoic (3-propylacrylic)[21]	/	/
3-Hexenoic (β,γ-hexenoic)[21]	/	/
p-Methyl-n-hexenedioic[25]	/	/
Main chain length of 6 carbon atoms		
Heptanoic (enanthic or oenanthic)[22]	/	/
Heptane(-1,7-)dioic (pimelic)[24]	/	/
Main chain length of 7 carbon atoms		
Octanoic (caprylic)[22,26–28]	/	/
2-Hydroxyoctanoic (2-hydroxycaprylic)[7]	0.02	0.02
3-Hydroxyoctanoic (3-hydroxycaprylic)[7,22,23,26]	0.01	0.01
7-Hydroxyoctanoic (7-oxidanyloctanoic)[7,25,26]	0.05	0.05
7-Oxo(keto)octanoic (7-keto-n-caprylic)[7]	Trace	Trace
8-Hydroxyoctanoic (8-hydroxycaprylic)*;[7,22,23,25–27]	3.1	6.5
Octane(-1,8-)dioic (suberic)[7,24]	Trace	0.1
Methyloctanedioic[25]	/	/
2-Octenoic[22]	/	/
7-Hydroxy-2-octenoic[7,26]	Trace	0.02
8-Hydroxy-2-octenoic[7,26]	Trace	0.1
2-Octenedioic (1-hexene-1,6-dicarboxylic)[7,26]	Trace	0.1
Methyloctenedioic[25]	/	/
Main chain length of 8 carbon atoms		
Nonanoic (1-octanecarboxylic or pelargonic)[21,22]	/	/
n-Nonanedioic[24,25]	/	/
9-Hydroxynonanoic (9-hydroxypelargonic)[25]	/	/
Main chain length of 9 carbon atoms		
10-Acetoxydecanoic[27]	/	/
Methyl 3-hydroxy decanoate†;[27]	/	/
3-Hydroxydecanoic*;[7,22,24–27,29]	0.9	1.5
6-Hydroxydecanoic[25,29]	/	/
9-Hydroxydecanoic[7,20–22,30,31]	0.2	0.5
10-Hydroxydecanoic*;[7,22,23,25–28]	13.0	17.6
3,9-Dihydroxydecanoic[26,29]	/	/
3,10-Dihydroxydecanoic*;[7,22,25–27,29]	4.4	7.8
5,10-Dihydroxydecanoic[25,27]	/	/
8,9-Dihydroxydecanoic[7,25,26]	0.1	0.4
9,10-Dihydroxydecanoic[25,27,29]	/	/
(1,10-)Decanedioic (sebacic)*;[7,22–27]	2.5	4.1
3-Hydroxydecanedioic[7,26,27]	0.01	0.1
n-Decanedioic[25]	/	/
2-Decenoic[11]	/	/
10-Acetoxy-2-decenoic[27]	/	/
8-Hydroxy-2-decenoic[7,26]	Trace	0.02
9-Hydroxy-2-decenoic*;[7,22,25,26,28]	1.2	2.5
10-Hydroxy-2-decenoic*;[7,22,23,25–27]	50.5	66.7
4,9-Dihydroxy-2-decenoic[29]	/	/
4,10-Dihydroxy-2-decenoic[29]	/	/
9,10-Dihydroxy-2-decenoic[7,29]	0.03	0.5
2-Decenedioic (1-octene-1,8-dicarboxylic)*;[7,22,23,26]	3.1	5.6
n-Decenedioic[25]	/	/
Main chain length of 10 carbon atoms		
11-Hydroxyundecanoic[21,25]	/	/
Main chain length of 11 carbon atoms		
10-Hydroxydodecanoic[7,23]	0.1	0.6
11-Hydroxydodecanoic[7,22,23,25–27]	0.3	0.8
11-Oxo(keto)dodecanoic[27]	/	/
12-Hydroxydodecanoic (12-hydroxylauric)[7,23,26]	0.1	0.4
3,10-Dihydroxydodecanoic[7,26]	Trace	0.03
3,11-Dihydroxydodecanoic[7,25–27,29]	0.1	0.4
3,12-Dihydroxydodecanoic[7,25,26]	Trace	0.1
9,10-Dihydroxydodecanoic[7]	Trace	0.1
10,11-Dihydroxydodecanoic[7,26,27]	0.01	0.2
10,12-Dihydroxydodecanoic[7,26]	Trace	0.1
11,12-Dihydroxydodecanoic[7,27,32]	Trace	0.1
Dodecane(-1,12-)dioic[7,23,26]	0.01	0.1
3-Hydroxydodecanedioic[7,26,27]	Trace	0.03
10-Hydroxy-2-dodecenoic[7,26,27]	Trace	0.1
11-Hydroxy-2-dodecenoic[7,26,27]	Trace	0.3
12-Hydroxy-2-dodecenoic[7,26,27]	Trace	0.2
11,12-Dihydroxy-2-dodecenoic[7]	0.01	0.05
2-Dodecenedioic (traumatic)[7,26,27]	Trace	0.03
Main chain length of 12 carbon atoms		
Methyltridecenedioic[25]	/	/
Main chain length of 13 carbon atoms		
Tetradecanoic (myristic)[7] + carbohydrate	–	–
12-Hydroxytetradecanoic[23]	/	/
13-Hydroxytetradecanoic[7,23,26]	Trace	0.1
14-Hydroxytetradecanoic[7]	0.02	0.04
3,13-Dihydroxytetradecanoic[7,25,26]	Trace	0.02
13-Hydroxy-2-tetradecenoic[7,23]	Trace	0.02

(*continued*)

Table 1. (Continued)

IUPAC (with or without other trivial) name and molecular size	*Relative amount*[7] *Min*	*Max*
Main chain length of 14 carbon atoms		
Hexadecanoic (cetylic or palmitic)[7,22,25]	Trace	0.1
15-Hydroxyhexadecanoic[23]	/	/
Main chain length of 16 carbon atoms		
Octadecanoic (cetylacetic, stearic or stearophanic)[7]	0.02	0.1
9-Octadecenoic (oleic)[7,25]	Trace	0.02
Main chain length of 18 carbon atoms		
Icosanoic (arachic, arachidic or eicosanoic)[7]	Trace	0.1
Main chain length of 20 carbon atoms		
Tetracosanoic (lignoceric)[7]	Trace	0.02
Main chain length of 24 carbon atoms		
II. Aromatic organic acids		
Benzenecarboxylic (benzoic)[7,21]	Trace	0.06
4-Hydroxybenzoic or p-hydroxybenzoic[7,25,26]	0.01	0.3
Phenylacetic (α-toluic or benzenacetic)[21,22]	/	/
1,3-Benzenedicarboxylic (isophthalic)[25]	/	/
3-(3-Hydroxyphenyl)propanoic (4-hydroxyhydrocinnamic)[7]	Trace	0.01
3-(3,4-Dihydroxy phenyl)-2-propenoic (caffeic)[7]	Trace	–
4-phenylbutanoate (phenylbutyrate)[†,33]	/	/
3-(4-Hydroxy-3-methoxy phenyl)propionic (benzenepropanoic)[27]	/	/
III. Nonaromatic organic acids		
2,3,4-Trihydroxybutanoic (threonic and isothreonic isomers)[7]	Trace	0.14
2,3,4-Trihydroxyglutaric (arabinoic)[7] + γ-lactone	Trace	0.09
2,3,4,5-Tetrahydroxypentanoic (ribonic)[7] + γ-lactone	Trace	0.4
Gluconic (dextronic)[7,26] + γ-lactone	0.7	1.4
1,3,4,5-Tetrahydroxycyclohexanecarboxylic (quinic)[7]	Trace	0.3

*Fatty acids dominant in RJ.

[†]Any salt of corresponding acid.

nr, compound was not registered; Trace, compound was determined below 0.01% of the total ion current of chromatograms; /, qualitative analysis of compounds in RJ was conducted whereas the quantitative was not; –, the presence of compounds in RJ was detected qualitatively, but not quantitatively; IUPAC, International Union of Pure and Applied Chemistry; RJ, royal jelly.

fatty acids, such as octane(-1,8-)dioic acid; and (6) methyl branched fatty acids, such as 2-methylbutanoic acid. Although some of these acids could be further divided into more than one subclasses of fatty acyls, such as 10-HDA that can be considered as either straight-chain or unsaturated or hydroxy fatty acid, the proposed fatty acids in RJ are for the most part well accepted. 10-HDA constitutes ~70% of lipid extracts from RJ and more than 50% of free fatty acids (90%–95% of total fatty acids) in RJ.[7,28,32,33] 10-HDAA as a precursor of 10-HDA constitutes ~15.9% of lipid extracts from RJ.[7] Both 10-HDA and 10-HDAA account for at least 60%–80% of total fatty acids in RJ.[33] Six additional fatty acids are also known to be dominant fatty acids in RJ, including 8-hydroxy octanoic acid (constituting ~4.9% of lipid extracts from RJ), 3-hydroxydecanoic acid (1.2%), 3,10-dihydroxydecanoic acid (5.9%), 9-hydroxy-2-decenoic acid (1.7%), 1,10-decanedioic acid (3.3%), and 2-decene (-1,10-)dioic acid (4.1%).[7]

Eleven fatty acid esters detected in lipid extracts from RJ include a diverse range of esterified moieties as follows: two cyclic esters, δ-octalactone, and δ-decalactone;[27] one phosphoric acid ester, 10-HDA phosphate;[28] two glucoside esters, the monoglucosides of 10-HDA and 10-HDAA;[32] and six random heterodimers, and heteropolymers usually through ester bonds, mono- and diesters of 10-HDA, in which the hydroxyl group is esterified by one unit of the four fatty acids (including 10-HDAA, 8-hydroxyoctanoic acid, 3,10-dihydroxydecanoic acid, and 2-decenedioic acid).[28]

A metabolic pathway for *de novo* biosynthesis of fatty acids in the mandibular glands of nurses was proposed based on proteomic analyses and deuterated analytes in gas chromatography–mass spectrometry.[6,30,35] For example, the biosynthesis of 10-carbon fatty acids in mandibular glands is accomplished in a three-step bifurcated pathway: branches at the last (ω) and second-to-last (ω-1) positions are first established by hydroxylation of octadecanoic acid at the ω and ω-1 positions; then through beta-oxidation, the spiral long-chain 18-carbon hydroxyl acids are shortened to principal 10-carbon hydroxylated components; lastly, the ω and ω-1 hydroxy groups on the components can be oxidized to give diacids and keto acids. To present further chemical features of these fatty acids in RJ, we consider the following points:

1. Long-chain fatty acids (with main chain length of more than 12 carbon atoms) in RJ are significantly less available than short- and medium-chain fatty acids (with main chain length of fewer than 6 carbon atoms and of 6–12 carbon atoms, respectively) among which most have 8, 10, and 12 carbon atoms in the main chain. The medium-chain fatty acids in RJ can be desaturated to form the corresponding monounsaturated acids, and further oxidized through the desaturase system to the corresponding dicarboxylic acids.
2. The largest subclass of fatty acyls in RJ is a family of mono- and dihydroxy carboxylic acids. Of these, there are eight chiral monohydroxycarboxylic acids present as a mixture of optical isomers, including 3-hydroxydecanoic, 3,9-dihydroxydecanoic, 3,10-dihydroxydecanoic, 4,9-dihydroxydecenoic, 4,10-dihydroxy-2-decenoic, 9-hydroxy-2-decenoic, 9,10-dihydroxy-2-decenoic, and 3,11-dihydroxydodecanoic acids.[28,29]

Thus, most fatty acids in RJ are medium-chain fatty acids, whether hydroxylated in terminal and/or internal positions, terminated with mono- or dicarboxylic acid groups, and saturated or monounsaturated at 2-position.

A minority of sterols in RJ. Besides the acids described above, lipids in RJ contain sterols in minor amounts. The composition of the sterols in pollen and RJ was found to be

Table 2. Sterols Detected in a Preparation of Sterols from Royal Jelly

Systematic (with or without other trivial) name	*Relative amount*[33] *Min*	*Max*
I. Cholesterol and derivatives		
Cholest-5-en-3β-ol (cholesterol)[7,33]	3.7	25.5
Cholest-24(24′)-ene-3β,5α,6β-triol[31]	/	/
Cholesta-5,24-dien-3-ol (desmosterol)[31]	/	/
Cholesta-5,24(24′)-dien-3β-ol-7-one[31]	/	/
Cholesta-5,24(24′)-diene-3β,7α-diol[31]	/	/
Cholesta-5,24(24′)-diene-3β,7β-diol[31]	/	/
II. Cholesteryl esters		
24-Methylene-cholest-5-en-3β-ol (24-methylenecholesterol)*:[11,27,31,33,36]	25.0	65.8
25-Hydroxy-24-methylenecholesterol or 25-hydroxy-24-methylcholesterol[7]	/	/
III. Phytosterols and derivatives		
24-Methylcholest-5-en-3β-ol or ergost-5-en-3β-ol (campesterol)[33]	—	—
24-Ethylcholest-5-en-3β-ol or stigmast-5-en-3β-ol (β-sitosterol)[7,27,31,33,36]	12.1	39.1
Stigmast-5-en-3β-ol-7-one[31]	/	/
Stigmast-5-ene-3β,7α-diol[31]	/	/
Stigmast-5-ene-3β,7β-diol[31]	/	/
Stigmastane-3β,5α,6β-triol[31]	/	/
24-Ethylcholesta-5,22-dien-3β-ol or stigmasta-5,22-dien-3β-ol (stigmasterol)[33]	Chr	7.7
24-Ethylidene cholest-5-en-3β-ol or stigmasta-5,24(28)-dien-3β-ol (δ5-avenasterol or isofucosterol)[27,31,33,36]	10.2	21.6
Stigmasta-5,24(28)-dien-3β-ol-7-one[31]	/	/
Stigmasta-5,24(28)-diene-3β,7α-diol[31]	/	/
Stigmasta-5,24(28)-diene-3β,7β-diol[31]	/	/
Stigmast-24(28)-ene-3β,5α,6β-triol[31]	/	/
3-Hydroxystigma-5,24(28)-diene[7]	/	/
24-Ethylidene cholest-7-en-3β-ol or stigmasta-7,24-28-dien-3β-ol (δ7-avenasterol)[33]	—	6.0

*A fatty acid dominant in the preparation.

Chr, compound was determined on the basis of chromatographic conditions in the previous work.

very similar qualitatively.[33] At least twenty-two free and esterified sterols have been detected in lipid extracts from RJ (Table 2).[7,11,27,31,33,36] These unique sterols, known to originate from plant sources, are generally classified into three subclasses as follows:[34] (1) cholesterol and derivatives; (2) cholesteryl esters, such as 24-methylene cholesterol (24MET); and (3) phytosterols and derivatives, such as isofucasterol. Among these sterols, four compounds were identified as isofucosterol derivatives, including stigmast-5,24(28)-dien-3β-ol-7-one, stigmast-5,24(28)-diene-3β,7β-diol and stigmast-5,24(28)-diene-3β,7α-diol (optical isomers), and stigmast-24(28)-ene-3β,5α,6β-triol.[27,31] However, relative amounts of individual components of sterols were found not to be very similar between pollen and RJ.[33] It is interesting that 24MET constitutes 49%–58% of total sterols in RJ, but only 5.9% of those in pollen.[36]

Lipids in RJ as preventive and supportive medicines for health

Potential inhibitors of cancer growth. Malignant (or cancerous) tumor in humans is an aggressive and invasive disease, in which an autonomously proliferating immortal cell clone continuously evolves to independence outside the body's control against invasion and metastasis. In spite of the fact that heterogeneous histogenesis of the devastating disease has not yet been elucidated, several direct and indirect mechanisms behind carcinogenesis are understood at least in part, including (1) stimulation of angiogenesis, (2) postacquisition of cancer cell proliferation and invasiveness, (3) creation of reversed pH gradients across the plasma membrane in malignant progression of tumor cells, and (4) impairment of tumor immune surveillance. The idea that fatty acids such as poly- and monounsaturated fatty acids may act as candidate antitumor agents is not entirely new.[13,37] High intakes of monounsaturated fatty acids are negatively associated with breast cancer.[38] *In vitro* pharmacological effects of some dominant fatty acids in RJ on the modulation of tumor growth can be summarized as follows: (1) 10-HDA exerts an inhibitory effect on vascular endothelial growth factor-induced angiogenesis in cellular models of tumor growth, partly by inhibiting cell proliferation and migration;[39] (2) 10-HDA,10-HDAA and (1,10-) decanedioic acid act as modulators of estrogen receptor functions in various cellular systems,[40] and their possible antitumor efficacy is through estrogen–receptor mechanism;[11,40] (3) only under acidic conditions, 10-HDA inhibits the development of transplantable mouse leukemia and three lines of mouse ascetic tumor;[13,39] and (4) 10-HDA promotes both phagocytic activity of macrophage and endogenous production of antitumor cytokine tumor necrosis factor.[41] Thus, lipids in RJ are a natural type of potential inhibitors of cancer growth.

Immune system modulators. Within the human immune system, fatty acids serve as a source of energy, structural components of cell membranes, and binding sites for intra- and intercellular proteins. Furthermore, they play a crucial role in lipid-driven signaling pathways implicated in cellular innate immune responses.[42] Dietary fatty acids can reduce the risks of many human chronic disorders with etiological origins of immune dysfunction and are among the safest and the most efficacious for the treatments of inflammatory and autoimmune disorders. Subclinical (or sub-health) disorder is defined by the World Health Organization as a state between healthy and disease, and describes a group of endogenous disorders in which some parts of body's immune system are inadequate to resist to infectious pathogens. Proteins in RJ have been claimed to possess immunomodulatory activity; however, efforts are made to characterize its lipid nutrients efficacies for restoring impaired immune functions.[18] In a study demonstrating that innate immune cells such as dendritic cells are designed to establish the first line of defense against microbial pathogens, 1-(2-methoxyethoxymethyl) 2, 3-(10-hydroxy2-decenoyl) glycerol, a

derivative of 10-HAD, was shown to protect deficient mice against a virulent *Salmonella typhimurium* challenge during the early stages of nonspecific immune responses.[16] The fatty acid derivative is thought to play an immunomodulatory role in the nuclear factor-kappa-B-signaling pathway in response to bacterial infection, leading to the onset and regulation of the innate and adaptive immune responses. Inflammatory autoimmune diseases are another group of endogenous disorders in which the body's tissues are attacked by its own immune system cells. In a study investigating the potential clinical value of 10-HDA in blocking aberrant expression of matrix metalloproteinases (or matrixins) in early rheumatoid arthritis, 10-HDA was shown to inhibit the expression of several members of the matrixin family in synovial fibroblasts isolated from synovial tissues of patients with the disease.[43] 10-HDA is thought to act on the inhibition of matrixins through stress-activated protein kinase-signaling pathways, having consequences in the integration of immune and metabolic responses. Thus, lipids in RJ are natural modulators of the immune system and may have efficacy in autoimmune disease intervention.

Alternative therapies for menopause. Menopause is caused by the natural loss of ovarian follicular function or the surgical removal of ovaries. Clinical and pathological features observed in patients with menopause are mostly attributable to the scarcity of circulating estrogens occurring in the menopausal transition. For decades, estrogen alone or in combination with progestins has been the therapy of choice for the relief of menopausal symptoms, as well as for the longer-term prevention of postmenopausal osteoporosis. As with all hormonal therapy medicines, the use of estrogens in treating menopause symptoms has common side effects, such as breast pain, and increased risk of breast cancer. Many menopausal women choose particular functional foods as acceptable alternatives to hormone replacement therapy for attenuating the increased risk of breast cancer.[44] Phytoestrogens are a structurally diverse group of plant-derived nonsteroidal compounds that possess estrogen-like activity. Over the past decades, there has been much interest in the use of phytoestrogens for menopause. RJ taken for reproductive health of women has been used to alleviate or even relieve menopausal symptoms.[45] Three dominant fatty acids and one sterol in RJ, 10-HDA, 10-HDAA, 2-decenoic acid, and 24MET, exhibit estrogenic activity, as evaluated by a ligand-binding assay for the estrogen receptor.[11] Thus, lipids in RJ may be a natural type of alternative therapy for menopause.

Skin-aging protectors. There are two types of skin-aging processes: intrinsic aging, which is mainly determined by genetic factors, and extrinsic aging, which is the result of all external factors in the environment (such as chronic exposure to solar radiation). In spite of the age-related differences between individuals of different ethnic backgrounds, both extrinsic and intrinsic skin aging share a common mechanism in oxidative stress by the accumulation of oxygen-free radicals. Oxygen-free-radical-induced breakdown of the skin collagen layer and failure to replace damaged collagens with newly synthesized molecules are central to the deleterious changes observed in aged skin. Therefore, rebuilding the skin's collagen matrix may be a useful approach to preventing skin aging, and dual pathways in collagen biosynthesis by fibroblast are thought to be activators of pleiotropic cytokines and inhibitors of destructive matrixins. 10-HDA was observed to stimulate normal human dermal fibroblasts cell lines and to produce transforming growth factor $\beta 1$, a multifunctional cytokine known to be an inducer of collagen synthesis.[19,46] 10-HDA was observed to decrease production of several members of the matrixin family secreted by dermal fibroblasts as well as by epidermal keratinocytes.[43]

It is well known that collagen synthesis is also affected by the decline in hormone expression with age, and the best-known decline is that of steroids. The most potent phytoestrogens can help promote collagen production, and thus dietary phytoestrogens in RJ could be hypothesized to be effective antiaging skin care ingredients in the absence of experimental data.

Additionally, promoting the normal turnover of skin cells may be another useful approach to prevent skin aging.[47–49] 10-HDA may exert protection against damaging oxygen-free radicals through mechanisms similar to those of its analogous glycolic acid. These mechanisms include stimulating new cells in skin to generate elastic fibers, protecting skin from oxidative damage, and increasing deposition of hyaluronic acid filler in the dermis.[19] Thus, lipids in RJ are potentially protective against skin aging.

Neurogenesis inducers. Neurodegenerative diseases, pathologically characterized by both massive neuronal loss and interneuronal and intraneuronal accumulations of fibrillary materials, are a group of progressive disorders in the central nervous system, among which Alzheimer's and Parkinson's diseases are the most representative forms. The two diseases result from different causes of neurodegeneration; however, cell death is a common mechanistic theme. Advances in the understanding of multipotent neural stem cells/progenitors in the mature central nervous system have raised hope that the progression of neurodegeneration in the patient's brain might ultimately become amenable to causal therapy. In a study on induction of neurogeneration from neural stem cells, 10-HDA was observed to increase the generation of neurons from progenitor cells in rat embryos.[20] Moreover, because it is shorter than docosahexaenoic acid in carbon chain length, 10-HDA might be more beneficial for neural stem cells *in vivo* than the *in vitro* model of primary culture due to its permeability across the blood–brain barrier.[20] Although a detailed understanding of the mechanisms for neural differentiation of progenitor cells into neurons remains to be elucidated, neurotrophic factors are required for maturation of new neurons and to enable them to withstand further degeneration. In an *in vivo* study that evaluated the role of neurotrophins in neurogenesis, oral administration of RJ in adult mice resulted in selective enhancement of neurotrophic factors and corresponding receptors at the level of mRNA expression in the hippocampus of the brains.[50] More importantly, 2-decenoic

acid ethyl ester, a derivative of 2-decenoic acid, has been proven to enhance mRNA expression of brain-derived neurotrophic factor in cultured embryonic cortical/hippocampal neurons and the injury site of the spinal cord.[51,52] Thus, lipids in RJ are a natural type of neurogenesis inducers.

CONCLUSION

Overall, the lipids in RJ are composed of mostly fatty acids, almost all of which are present as free fatty acids with few being esterified. Most fatty acids in RJ are medium-chain fatty acids, whether hydroxylated in terminal and/or internal positions, terminated with mono- or dicarboxylic acid groups, and saturated or monounsaturated at the 2-position. Besides these fatty acids, lipids in RJ contain sterols in minor amounts. Lipids in RJ as preventive and supportive medicines for health are recommended, with potential activities, including inhibition of cancer growth, immune system modulation, management of menopausal symptoms, skin-aging protection, neurogenesis induction, and more. Taken together, the data indicate that the health-protecting properties of RJ can be, in part, ascribed to roles of lipids in RJ.

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AUTHOR DISCLOSURE STATEMENT

The authors declare that no conflict of interest exists.

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