REVIEW

Medicinal properties of jojoba (*Simmondsia chinensis*)

Zipora Tietel, Shirin Kahremany, Guy Cohen and Navit Ogen-Shtern

Department of Food Science, Gilat Research Center, Agricultural Research Organization, MP Negev 8531100, Israel; The Skin Research Institute, The Dead-Sea and Arava Science Center, Masada, 86910, Israel; Ben Gurion University of the Negev, Eilat Campus, Eilat 8855630, Israel

ABSTRACT

Jojoba, *Simmondsia chinensis* (Link) C.K. Schneider is an evergreen shrub widely grown in Israel, the Middle East, South America, Africa, India and Australia used as an agricultural crop for commercial purposes and as a source of its non-edible natural wax. It is widely used in pharmaceutics and cosmetic formulation due to its unique structural characteristics and beneficial health effects. In addition, extensive work has been published on the plant’s health-promoting activities, ranging from antioxidant activities to the treatment of cancer. Being a rich source of natural liquid wax, the majority of research regarding jojoba focuses on its applications, as well as on the ability to exploit the residual plant materials obtained in its production. To date, several potent phytochemicals have been attributed to its medicinal properties, e.g. simmondsin and phenolic compounds. The current review emphasizes the evidence-based medicinal qualities of the wax and plant extracts and highlights the gaps of knowledge in these research areas and the importance of acquiring additional understanding of jojoba distinctive traits.

Introduction – Jojoba, the desert gold

Jojoba, *Simmondsia chinensis* (Link) C.K. Schneider (Fig. 1), is an evergreen dioecious shrub growing in arid and semi-arid areas. This desert shrub can be grown in harsh, low irrigation and high-temperature environment (Ash et al. 2005), and it is tolerant to various environmental conditions (Kumar et al. 2012; Arya & Khan 2016). Taxonomically, it is the single member of the Simmondsiaceae family (Chase et al. 2016). The plant is native to Baja California and the Sonoran Desert in north-central Mexico and the southwestern United States. It was first mentioned in the literature by the Mexican historian Clavijero (1789) as a plant used by native-Americans in Baja California for its medicinal properties and as currency for the exchange of goods. A number of botanists, the first of whom was Link, presented initial descriptions of the plant and granted it its scientific name and taxonomic classification (Daugherty et al. 1958). Since the 1930s, jojoba has been scientifically studied. Research intensified during the 1950s, when jojoba wax was suggested as a substitute for banned whale sperm oil, and commercial interest in jojoba as a new agricultural industry emerged (Benzioni 2010). Due to its similarity to whale sperm oil, it was originally used mainly as a renewable non-animal substitute for industrial needs (Gisser et al. 1975). First successes in domesticating jojoba occurred in California and Arizona in the late 1960s and shortly after also in Israel (Benzioni 2010).
Genetics and diversity

Being a dioecious plant, the genetic variability of jojoba is translated into hundreds of cultivated clones, which hinders obtaining homogenous desired features such as the quantity of seeds, and the quality and yield of the liquid wax. Hence, the majority of cultivation is performed using vegetative propagation of mother plants, which reduces genetic variability but paradoxically leads to genetic vulnerability (Al-Obaidi et al. 2017). In light of this, it is especially important to understand the genotypes responsible for the quality of jojoba propagation and the content of jojoba seeds, as well as additional compounds. Several studies were published in this regard. Of these, few demonstrated variability in the content and quality of jojoba oil, and additional compounds, such as simmondsin (will be later elaborated) content among different jojoba genotypes (Benzioni et al. 2005; Al-Soqeer et al. 2012). In parallel, several methods for detecting genetic polymorphism and providing genotypes with molecular fingerprinting have been published and described in more detail in (Al-Obaidi et al. 2017). Clearly, it is still worthwhile to place great emphasis on understanding the genetics of jojoba. In addition, the impact of cultivation seems to play a key role in its variable yields (Atteya et al. 2018; Khattab et al. 2019).

Market and usages

The uniqueness of the jojoba plant stems from the unusual presence, amount, and chemical structure of liquid wax in its seeds, which consists of approximately 50% of the seed weight (Al-Widyan & Al-Muhtaseb 2010). Jojoba wax, also termed jojoba oil, is comprised of long-chain esters. These can be exploited in several industrial applications, most prominent are pharmaceuticals and cosmetics, due to the structural resemblance with human skin sebum and structural properties. Additional industrial uses that previously utilized whale sperm oil take advantage of jojoba oil in the production of plastics, detergents, renewable energy, and lubricants (Al-Widyan & Al-Muhtaseb 2010; Sandouqa & Al-Hamamre 2019; Vaillant et al. 2019). As a high yielding non-edible oil, its use as a raw material for the creation of biodiesel has been considered (Sandouqa & Al-Hamamre 2019). Of note, jojoba oil global production is growing rapidly, and has already exceeded 15,000 tons (2018) and is expected to reach 22,000 tons by 2022 (Worldwide analysis on the jojoba oil market; Bilin et al. 2018). This tremendous growth may be due to market demands, or alternatively, suggests an uncontrolled increase that will result in consequent over-supply, emphasizing the need to develop novel jojoba-based products and usages.

Aside from the oil, other parts of the jojoba plant possess properties that may become valuable (Wisniak 1994), e.g. jojoba meal and leaves were found to have various other potential uses. The meal is rich in proteins and fibers, and as such, has the potential to be used as food or staple feed. However, it contains anti-nutritional factors, a problem that still has to be industrially overcome (Reddy & Chikara 2010). The meal was also suggested as an anti-rodent agent (Al-Obaidi et al. 2017). In addition, leaves were found to possess potential medicinal properties, as further described in detail below. From an ecological perspective, the plant can also contribute to combat desertification due to its ability to grow in arid areas (Al-Obaidi et al. 2017). Like its usages, jojoba-based analyses can be roughly divided into two main sections: evaluation of its liquid
wax and identification of phytochemicals in other plant parts, including the jojoba meal obtained following the extraction process.

**Oil extraction methods and concomitant composition**

As mentioned earlier, jojoba wax is comprised of approximately 50% seed weight. However, to obtain pure oil, several steps are required. After the initial harvest, jojoba seeds are first cleaned to remove rough debris, such as dust and leaves, and are then typically left to dry and dehull (Arya & Khan 2016). To obtain a high yield, a combination of mechanical pressure and chemical extraction using hexane (or other organic solvents) is necessary (Wisniak 1994). The downside of this process is the environmental impact and economic price of the organic solvent. Usage of other solvents, such as chloroform and isopropanol has been tested and found to be less efficient and occasionally with leftover traces in the oil (Wisniak 1994; Abu-Arabi et al. 2000). Supercritical CO2, which is a solvent-free method, showed similar or higher oil yield, however, typically its initial establishment price is high. In addition to its pre-mentioned disadvantages, solvent extraction also results in lower quality wax. Thus, jojoba oil is currently mechanically extracted by cold-press method, at low heat, to conserve its quality characteristics, e.g. tocopherol contents (El-Mallah & El-Shami 2009). Naturally, the oil yield of this method is relatively low, as some oil is retained in the meal (Kibbutz Hazerim, personal communication), but the resulting wax is of high quality.

Jojoba oil is a mixture of long-chain (C36-C46) esters of fatty acid and fatty alcohol, distinguishing it from other vegetable oils, which are triglyceride-based (Figure 2) (Mokhtari et al. 2019). This gold-yellow odorless oxidation-resistant wax is liquid at room temperature, which is another unique characteristic differentiating it from other natural waxes used in cosmetics (Le Dréau et al. 2009; Zięba et al. 2015).

Meticulous analysis demonstrated that the main fatty chains composing the wax are C20:1 and C22:1 of both acids and alcohols, with changes of the exact percentage linked to both genetic and environmental factors (Busson-Breysse et al. 1994; Agarwal et al. 2018). Trace elements have also been reported in the wax (Agarwal et al. 2018). Free fatty acids, also present in the wax, are negatively correlated with wax quality (El-Mallah & El-Shami 2009). Tocopherols and phytosterols, two other groups of bioactive medicinal molecules, have also been observed in jojoba oil. Tocopherols are common in oil crops, serving as lipophilic antioxidants and oil stabilizers that also possess health-promoting properties. In jojoba oil, they were reported at relatively high concentrations of 417 ppm, with gamma-tocopherol as the main form (79.2%), and alpha, beta and delta-tocopherol at lower concentrations (El-Mallah & El-Shami 2009). Phytosterols are another group of characteristic compounds of oil, with structural resemblance to cholesterol. Thus, their consumption is recommended as cholesterol-lowering treatment. In jojoba, various types were recorded, including sitosterol, campesterol and stigmasterol (Busson-Breysse et al. 1994; Ogbe et al. 2015)

Chemical parameters for wax quality analysis have not been established yet, although such parameters are very common in other oil crops, e.g. olive oil. Quality grading might allow growers to receive better compensations for their high-quality wax.

**Jojoba meal and other plant part**

The remaining cake after oil extraction process (jojoba meal) is rich in dietary fibers and proteins.
However, the presence of simmondsin, a unique jojoba secondary metabolite and a principal bioactive component of jojoba, and its derivatives, prevents its use as food or animal feed purposes. Simmondsin, 2-(cyanomethylene)-3-hydroxy-4,5- dimethoxycyclohexyl-beta-D-glucoside (Figure 3) is present in seeds, hulls, leaves, twigs and roots of jojoba. Approximately 5% of jojoba meal is simmondsin with additional 0.5–1% of derivatives, of which the 2'-ferulate is the main one. Isolated and characterized by Elliger et al. almost thirty years ago, this unique molecule is toxic at high concentrations and has an anorexic action at lower levels (Elliger et al. 1973). Due to its cyano group, it is listed as an antinutritional compound and thorough removal of its content is required prior to usage as animal feed. Thus, several methodologies have been investigated for the neutralization/removal of this agent prior to usage as feed supplements, including chemical and enzymatic approaches (Verbiscar et al. 1981; Bouali et al. 2008; Elsanhoty et al. 2017). However, usage of simmondsin at low and at non-toxic range may be harnessed as a health-promoting agent as specified below. Unlike its well-characterized oil, other parts of jojoba plant are yet to be fully explored for their phytochemical composition. So far, research was mainly performed on simmondsin and derivatives, and on selected bioactive polyphenolic compounds (described below). To date, comprehensive in-depth metabolomic evaluation of the leaf, roots, twigs and meal is still lacking and therefore other unique compounds may be discovered in the near future.

Medicinal properties

Antioxidant capacity

When evaluating the medicinal properties of a plant, one of the most basic and simple characterizations relies on the evaluation of its antioxidant capacity and total phenolic content. Indeed, several studies have evaluated jojoba antioxidant activity with various methods and extraction methodologies.

Kara has evaluated the scavenging capacity of methanolic and ethanolic extract of both the seed and leaf of jojoba by the 2,2′-Diphenyl-1-picrylhydrazyl (DPPH) method (Kara 2017). This colorimetric method uses a stable free radical, which becomes discolored in the presence of an anti-oxidant, either transferring an electron or donating hydrogen (Brand-Williams et al. 1995). In this system, all jojoba extracts were found to possess similar scavenging efficacy (approximately 40% at 500 µg/ml). However, when determined by linoleic acid bleaching assay, the antioxidant activity of the methanolic and ethanolic leaf extracts was twice as much as those measured for the seeds (45 nmol/g). These conflicting results may be due to the inherent difference between the methods and the favor of lipophilic moieties in the second system. An interesting study by Wagdy et al. investigated the possible usage of the seed hull extract and found a considerable scavenging effect in similar methodologies described above (Wagdy & Taha 2012). This approach is of high interest, as typically the hulls are a waste product of jojoba wax production, while these authors showed that the hulls may provide additional value in the industry. The impact of cultiva-
tion conditions on the antioxidant properties has also been investigated, and it was reported that jojoba antioxidant activity of the methanolic leaf extract could be increased by 50% in enriched cultivation conditions (addition of putrescine and Moringa extract) in comparison to control conditions (Taha et al. 2015).

Abdel-Wahhab et al. investigated the hepatoprotective impact of jojoba ethanolic seed extract in vivo. Both low and high dosage (0.5 and 1 mg/kg, respectively) attenuated liver oxidative stress in mycotoxin-induced damage model. Malondialdehyde (MDA) levels, an important ROS-derived lipid peroxidation product of polyunsaturated fatty acids, was doubled in the mycotoxin group but dropped upon jojoba treatment. Concomitantly, the liver levels of the anti-oxidant enzyme superoxide dismutase (SOD) were raised to those of the control group (Abdel-Wahhab et al. 2015). However, these impressive results may not be exclusively attributed to direct jojoba antioxidant capacity, and can result from secondary action of jojoba extract, as it also reduced inflammation and hepatocellular necrosis in that model (Abdel-Wahhab et al. 2015).

The majority of studies regarding jojoba do not pinpoint the active compound assigned for the antioxidant capacity of the above-mentioned extracts. In-depth chemical analysis is still required in order to gain insight into the active molecule or molecules. A comprehensive work was performed by Abdel-Mageed et al., identifying flavonoid aglycones from the ethanolic leaf extract of jojoba (Abdel-Mageed et al. 2014). Quercetin 3-methyl ether (isorhamnetin), quercetin 3,3-dimethylether, and quercetin showed strong antioxidant activity and lipoxygenase inhibition (Fig. 4). In a recent study conducted in hyperglycemia-induced oxidative stress model, it was found that simmondsin, one of the principal bioactive components in jojoba mentioned above, is sufficient to reduce pancreatic beta-cell damage, which may explain the protective antioxidant properties of jojoba extract. The contribution of tocopherol on the antioxidant capacity of the oil should also be evaluated. The collective results demonstrate that mainly leaf and hull extracts of jojoba, may possess strong antioxidant properties that can be used as a remedy for oxidative stress-related pathologies. However, it should be noted that the safety of such extracts should be clinically validated for both their safety and efficacy prior to usage as food supplements or other health-promoting products.

**Anti-fungal and anti-microbial properties**

New antimicrobial agents are of constant need due to the rise in antibiotic-resistant germs. The hypothesis that jojoba may present such properties has been investigated by several research groups. Jojoba extracts derived from hulls (extracted in 80% methanol, ethanol,
acetone, isopropanol and ethyl acetate) showed significant anti-bacterial properties (Wagdy & Taha 2012; Escherichia coli, Staphylococcus aureus, Bacillus cereus, Listeria monocytogenes and Salmonella typhimurium growth was inhibited in various degrees of efficacy. The authors suggested that this phenomenon is in correlation with ethnobotanical knowledge. However, the active molecule(s) or mechanism of action (MOA) were not elucidated in this preliminary evaluation. Abu-Salem and Ibrahim have also shown high efficacy on both bacteria and fungi of root extract and latex of the plant (Abu-Salem & Ibrahim 2014). In separate works, antibacterial and antifungal activities were also found for jojoba oil (Pooja Umaiyal et al. 2016; Al-Ghamdi et al. 2019). Thus, it seems that the active agent(s) are not restricted to a specific part of the plant. However, it is important to mention that several other reports evaluating similar extracts found no noticeable antimicrobial activity. This discrepancy may be due to the bacterial strains used, as well as the cultivating and genetic differences between the plants (Elnimiri & Nimir 2011; Al-Qizwini et al. 2014). In addition, although all researchers used routine evaluation systems (agar diffusion assay, disc diffusion assay and minimal inhibitory concentration (MIC)), these models may be different between laboratories and any modification may affect the obtained results significantly (Balouiri et al. 2016).

In a very interesting examination, the two glucosides, simmondsin and simmondsin 2-ferulate have been isolated form jojoba, and tested for their bioactivity (Abbassy et al. 2007). In that study, both agents showed high efficacy with moderated potency (Half maximal effective concentration (EC50) of approximately 150 mg/l) against plant pathogenic fungi. Similar studies are required in order to attribute the antimicrobial properties to simmondsin, its derivatives, and other compounds.

**Dermatology and skin care**

The skin is a vital homeostatic organ that acts as a physical, chemical, and biological barrier (Gvirtz et al. 2020; Kahremany et al. 2020). As chronically exposed to deleterious actions of the environment, its appearance may be affected and extrinsic aging of the skin may become visible (Choi 2019; Ogen-Shtern et al. 2020). Jojoba oil has long been used in dermo-cosmetic products. Amongst its main functions, jojoba is a key component of the oil phase in numerous topical formulations (Di Berardino et al. 2006). In addition to its structural importance to the formulation stability, jojoba oil also serves as a carrier and enhancer of the active compounds (Nasr et al. 2016). In addition, the antioxidant and tocopherol content of jojoba mentioned above may be used to reduce skin-related oxidative stress (Kahremany et al. 2019). However, it should be noted that jojoba can also exert contact dermatitis (Wantke et al. 1996; Di Berardino et al. 2006) and may be absorbed systemically if high topical amounts are applied (Yaron et al. 1980; Matsumoto et al. 2019).

Numerous dermo-cosmetic products use jojoba as part of their formulation and to date, almost 200 International Nomenclature of Cosmetic Ingredients (INCI) entries are listed with jojoba and derivatives. However, its beneficial potential as an active agent in skin care has not been thoroughly investigated, including the lack of large control trial supporting its effectiveness while used in massage, a key end-usage in the current jojoba oil market.

Several clinical cosmetic trials have investigated the properties of jojoba dermal applications. For instance, it was reported that the addition of jojoba hydrolyzed ester to lotions can enhance skin hydration by reduction of trans-epidermal water loss (TEWL) (Meyer et al. 2008). In a separate study, increasing concentrations of jojoba oil in cream formulations enhanced their moisturizing properties (Zięba et al. 2015). Nevertheless, it is exceedingly difficult to elucidate the impact of jojoba in this setup, separating its impact from the rest of the formula. Thus, to evaluate whether this liquid wax has direct action on epidermal and dermal layers, a more direct approach is of need. To address this, Ranzato et al. have used the scratch assay, in which a wound is inflicted by a tip on dermal keratinocytes and fibroblast cell monolayers (Ranzato et al. 2011). Their data demonstrated that jojoba wax is safe at a wide range of concentrations and may enhance wound closure in both keratinocytes and fibroblasts cultures. They also have shown that jojoba treatment triggers collagen synthesis in fibroblasts. Ca2+ dependent mechanism that requires the involvement of the PI3K–Akt–mTOR pathway and of the p38 and ERK1/2 was suggested by the authors.

Interestingly, the beneficial impact of jojoba oil on psoriasis has also been suggested (Pazyar & Yaghoobi 2016). This chronic inflammatory skin disease is typically displayed as plaques, covered with thick, silvery, shiny scales that hampers the quality of life of the patients (Rendon & Schäkel 2019). El Mogy suggested
that jojoba oil without or with 2% salicylic acid can improve psoriatic skin (El Mogy 2005). In two clinical trials, jojoba oil-based microemulsion was used as a platform for enhancing the action of commercial drugs (Nasr et al. 2016; Ramez et al. 2018). Further in vitro and clinical studies are required to understand the potential use of jojoba in psoriasis.

Acne-prone, lesioned skin is the result of combined excessive sebum production, bacterial settlement, and inflammation. Results of a study by Meier et al. show that treatment with jojoba oil clay facial masks can reduce pustules, papules, cysts and comedones (Meier et al. 2012). Importantly, the study demonstrated the impact of dermatological conditions on quality of life at a cost-effective treatment regime. Other animal-studies experiments, demonstrating anti-inflammatory action of jojoba oil (see below) may also be relevant to the effect on acne.

**Metabolic syndrome and metabolism**

The metabolic syndrome is a set of metabolic abnormalities such as insulin resistance, nonalcoholic fatty liver disease, glucose intolerance, obesity and type 2 diabetes. A recent study by Belhadj et al. demonstrated that incorporation of jojoba seed in the diet of rats might reduce the deleterious effects of a high-fat diet and high fructose diet (Belhadj et al. 2020). In their study, a marked reduction was observed in insulin resistance, fat mass and renal complications in the treatment group. These findings were accompanied by reduction in the rat body mass, and thus the author concluded that this anorexic impact is the main cause of the jojoba regimen. Their results are also in line with previous studies demonstrating that jojoba leaf extract may reduce body weight in rats (Makpoul et al. 2017). Interestingly, simmondsin, present in both jojoba oil and leaf extracts, has already been shown to reduce food intake in rats, suggesting that the impact of jojoba on appetite is mediated by this unique molecule (Cokelaere et al. 1995). In addition, a direct effect of simmondsin was observed in pancreatic beta-cells, suggesting a multi-site action of the molecule (Belhadj et al. 2018).

**Additional medicinal values and the future of jojoba research**

Other scattered reports have shown additional health beneficial impacts of jojoba oil and extracts. For instance, jojoba has been reported to possess anti-inflammatory properties, both *in vitro* and *in vivo* (Habashy et al. 2005). This may be linked to the ability of the plant extract and simmondsin to inhibit with high potency both lipoxygenase (LOX) and cyclooxygenase (COX), key enzymes in the inflammation cascade. LOX and COX are responsible mainly for the metabolism of arachidonic acid, generating its downstream signaling and inflammatory mediators, such as prostaglandins, leukotrienes and lipid peroxidation by products (Cohen et al. 2013; Abdel-Mageed et al. 2014, 2016). Furthermore, jojoba leaf extracts at as low as EC<sub>50</sub> 2 µg/ml have been reported to present an anti-viral effect on herpes simplex viruses type 1 and 2 (HSV-1, HSV-2) and varicella-zoster virus (Yarmolinsky et al. 2010). Anti-cancer cytotoxicity was also demonstrated in human melanoma (MV 3), breast (MCF 7), and colorectal (HCT 116) tumor cell lines as well as inhibition of angiogenesis, required for tumor growth (D’oosterlynck & Raes 2008; Al-Qizwini et al. 2014; Al-Obaidi 2019).

Generally, jojoba usage may be separated roughly into two branches: the use of its unique oil, and the use of extracts obtained from other parts of the plant. Currently, the jojoba liquid wax is mainly used as a substrate for the formulation or as an ingredient with an active role. However, as it was demonstrated, the whole plant, including leaves, roots and hulls can be used as a source of bioactive molecules and this direction should also be developed. A thorough investigation using metabolomic tools may reveal more unique active compounds. Another difficulty in jojoba research is the current scarcity of commercially available simmondsin and derivatives, thus more sources are of need in order to understand the entire pharmaceutical potential.

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