

# Unraveling the beneficial effects of herbal Lebanese mixture “Za’atar”. History, studies, and properties of a potential healthy food ingredient

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## ABSTRACT

Interest in plant-based food has grown in recent years due to their primary prevention potential. Za’atar, an ancient and popular Lebanese herbal mixture, might disclose relevant clinical interest, due to the well-known intrinsic properties of its individual components. Za’atar mixture contain *Origanum syriacum* (Lebanese thyme), *Thymbra spicata* (Wild thyme), *Rhus coriaria* (Sumac), and *Sesamum indicum* (Sesame). Here we explored the history, composition, general employment, and bio-active aspects of Za’atar through available *in vitro*, animal, and clinical trials evidence to depict its possible role as an innovative nutraceutical tool. The combined action of Za’atar constituents is able to generate comprehensive beneficial effects on several common pathogenic pathways underlying chronic cardio-metabolic diseases and cancer. However, main available evidence derives from animal and *in vitro* studies. Thus, further human studies are needed to fully characterize Za’atar as a preventive and curative tool.

## 1. Introduction

The link between nutrition and health is acknowledged since ancient times. Hippocrates said, “Let food be your medicine and let medicine be your food”, and recently the consumers are increasingly aware of potential benefits of certain foods and/or food components to prevent or cure several diseases. Although the ultimate translational value of some beneficial effects of foods and/or food components tested *in vitro* is often lacking, the demand for health-promoting products has progressively increased in the 21st century, with number of published papers on this topic increasing from 500 to about 5,000 yearly between 2000 and 2020. Beside foods and/or food components of healthy diet, the public opinion is also becoming aware that adequate lifestyle has a critical role in achieving optimum health goals (WHO, 2020).

The term “functional food”, firstly introduced in Japan in the late 1980s, refers to foods or ingredients to be providing additional benefits

beyond the general benefits of nutrient intake and satisfaction of hunger (Bigliardi & Galati, 2013; Weststrate, van Poppel, & Verschuren, 2007). “Nutraceutical” is also used as term to indicate a food or part of a food which may provide health benefits, including prevention and treatment of disease. In this regard, a vast number of foods with potential nutraceutical effects have been studied (Lenssen, Bast, & de Boer, 2018). For example, cocoa and dark chocolate, which are enriched in polyphenols, provide beneficial effects due to antioxidant and anti-inflammatory properties (Corti, Flammer, Hollenberg, & Lüscher, 2009; Montagna et al., 2019), and stimulation of gastrointestinal motility (Caponio et al., 2020).

Food ingredients of vegetal origin raise the interest of food industry with the increase in demand on “natural” ingredients. Vegetables and vegetable-based products contain notable levels of bioactive compounds as carotenoids, phenolic compounds (PC), fiber, and vitamins (Lemmens et al., 2014; Shashirekha, Mallikarjuna, & Rajarathnam, 2013). Most of these compounds show antioxidant properties and health benefits as

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**List of abbreviations**

AMPK	Adenosine monophosphate-activated protein kinase
CVD	Cardiovascular disease
CVL	Carvacrol
EVOO	Extra virgin olive oil
FAS	Fatty acid synthase
FDA	Food and Drug Administration
FFA	Free fatty acids
GA	Gallic acid
GPX	Glutathione peroxidase
H <sub>2</sub> O <sub>2</sub>	Hydrogen peroxide
HbA <sub>1c</sub>	Glycated haemoglobin A <sub>1c</sub>
HDL-C	High-density lipoprotein-cholesterol
HFD	High fatty diet
hs-CRP	High-sensitivity C-reactive protein
INOS	Inducible nitric oxide synthase
LDL-C	Low-density lipoprotein-cholesterol
LPS	Lipopolysaccharide

MD	Mediterranean Diet
MDA	Malondialdehyde
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic steatohepatitis
NF-κB	Nuclear factor κB
NO(x)	Nitrates/nitrites
PA	Palmitic acid
PC	Phenolic compounds
PUFA	Polyunsaturated fatty acids
RA	Rosmarinic acid
ROS	Reactive oxygen species
SOD	Superoxide dismutase
SREBP-1	Sterol regulatory element binding protein-1
TBARS	Thiobarbituric acid-reactive substances
TC	Total cholesterol
TG	Triglycerides
TNFα	Tumour Necrosis Factor alpha
VOO	Virgin olive oil

decreasing cardiovascular risk with beneficial outcomes on primary and secondary prevention of chronic, noncommunicable diseases, including cancer (Fiedor & Burda, 2014; Gowd, Karim, Shishir, Xie, & Chen, 2019; Shahidi & de Camargo, 2016).

Mediterranean Diet (MD) is considered as one of the healthiest dietary habit (Serra-Majem et al., 2019). It is the best-studied and most evidence-based diet able to prevent and/or treat several diseases, including non-alcoholic fatty liver diseases (NAFLD), obesity, diabetes, inflammation, and cancer (Shaikh, Braakhuis, & Bishop, 2019). In general, MD implies the high intake of vegetables and fruits providing fiber, vitamins, and antioxidants such as phenolic compounds, which may be responsible for protective effects on risk factors (Schwingshackl, Morze, & Hoffmann, 2019).

In this context, specific interest derives from the analysis of ancient, popular foods, widely employed as a part of local culture and history. In particular, the Lebanese herbal mixture “Za’atar” should be considered a healthy food ingredient due to the combined presence of several bioactive compounds with possible beneficial outcomes on human health, as shown by *in vitro*, *in vivo*, and clinical studies. However, to date, no studies have described the bioactivity of the whole Za’atar mixture. The available set of studies on single component and/or single bioactive compounds of Za’atar, provides substantial evidence of its beneficial effects. As illustrated in Table 1, here, we review several aspects of “Za’atar” in terms of history, medicinal chemistry, and properties as a potential health-promoting food and/or food ingredient discussing the health benefits of single components in a technical approach. For this purpose, we discussed several cellular, animal, and clinical evidence, combining the cultural/traditional profile of food with stronger scientific evidence.

## 2. Za’atar - history and general aspects

Lebanon covers an area of 10,452 km<sup>2</sup> in the Eastern Mediterranean region with diverse climatic and ecological properties that are unique among other countries of the region, making it as a center of plant biodiversity (Safaa Baydoun, Lamis Chalak, Helena Dalleh, & Nelly Arnold, 2015). Lebanon hosts over 2,600 terrestrial plant species with a high rate of endemism (12%), including 8.5% as broad endemics (Lebanon, Syria, and Palestine) and 3.5% as narrow endemics to Lebanon (UNDP, 2019). In spite the increased use of synthetic chemical drugs, Lebanese citizens tend to choose natural products and mainly local medicinal plants as home remedies for treatment and/or prevention of a wide range of diseases, as well, some of those “healthy” plants

are included on their diet (M. Khalil et al., 2020; Khoury, Stien, Eparvier, Ouaini, & El Beyrouthy, 2016b; S. Baydoun, L. Chalak, H. Dalleh, & N. Arnold, 2015). As an example, herbal tea is used in herbal formulations and herbalist preparations, and it is considered as “treatment of choice” for several diseases including headaches, stomachaches, abdominal pain, microbial infections, asthma, coughs, pulmonary and urinary disorders (Safaa Baydoun et al., 2015; Loizzo et al., 2008). In fact, the common notion and concept among many Lebanese people is “If it doesn’t cure, it will not harm” to justify the vast use of plant in traditional medicine (Gali-Muhtasib, Hilan, & Khater, 2000).

Manakish (Arabic: مناقيش, pronunciation: manāqish, singular: “mankousheh” is the most favorite and popular breakfast among Lebanese people. By description, it is a round flat bread covered with a mixture of Za’atar, mixed with local olive oil and baked in the oven (CIHEAM-MAI.B, 2008) “Za’atar” as a word, has several meanings that may differ with different cultures and in which the dialects and terms vary. Basically, “Za’atar” refers to a type of plant as well as to a combination of different plants and spices blended all together. In Lebanon, “Za’atar” refers to many species belonging to different plant families called *thyme-like* plants, which are enriched in carvacrol (5-isopropyl-2-methylphenol) (CVL) and thymol, two isomers of phenolic “monoterpenes”, that give the unique smell of these plants (Mohamad Khalil, Hala Khalifeh, et al., 2020). *Thyme-like* plants include *Origanum*, *Satureja*, *Thymbra*, and *Thymus* plant genera, all sharing similar uses and aromatic flavor profile. These plants are indigenous to Lebanon and the Mediterranean area, where they have grown for thousands of years and in different geographic territories (Al Hafi et al., 2017). (Soomro, 2019).

The Ancient book “*A-lma’tmd fi al-a’douiah al-mfrdah*” (English translation: The approved book in single drugs) is a summary of a broad collection of valuable medicinal books. It describes medicinal plants and herbs shedding the light on their benefits, as well as the possible extracted medicines from each of them. The textbook depicts the recognized name of each herb or plant, where it grows, its shape, color, the diseases that can be treated, and the extracted medicine. In this book, Za’atar (or Sa’atar) has been reported as a different and “famous” class of edible and medicinal herbs including wild or mountainous Za’atar, with different properties regarding the leaf morphology, thickness, and color. The book stated that these herbs possess similar characteristics, and this similarity includes the medical uses, especially for the treatment of gastrointestinal illnesses. Specifically, these herbs protect the intestinal mucosal barrier, reduce abdominal pain, relieve the stomach and the gut wall, and help in keeping the stool moist. Also, the book stated that these plants act beneficially in protecting the

**Table 1**

History, traditional use, phytochemicals, and scientific-based evidence of Za'atar mixture components.

Component Scientific / local name	History/traditional use	Major chemical/ phytochemical composition	Scientifically-based bioactivity
<i>Origanum Syriacum/ Za'atar</i>	Bible hyssop	Polyphenols:	Antibacterial effects
	Fresh leaves are used in salad	Rosmarinic acid	Antioxidant and anti-inflammatory activities
	Dried leaves are used in herbal tea	Essential oils: Carvacrol and thymol	
<i>Thymbra spicata/ wild Za'atar</i>	Arial parts are used for water distillation	Fiber	
	Spicy Za'atar	Polyphenols:	Antibacterial effects
	Fresh and pickled leaves are used in salad	Rosmarinic acid, flavonoids	Antioxidant and anti-inflammatory activities
	Dried leaves and flowers are used in herbal tea	Essential oils: Carvacrol	Anti-steatotic effect
		Fiber	
<i>Rhus coriaria / Sumac</i>	Sicilian sumac	Polyphenols: Gallic acid (and derivatives), flavonoids and anthocyanins	Antimicrobial effects
	Dried fruits are used as spicy	Fatty acids	Antioxidant and anti-inflammatory activities
		Mineral and vitamins	Anti-diabetic, hypolipidemic, hypercholesterolemic effects
<i>Sesamum indicum/ Sesame</i>	Oldest oilseed plant	Fiber	
	Fresh and toasted seeds are used as food ingredient	Fatty acids	Antioxidant and anti-inflammatory activities
	Sesame oil is used in food and folk medicine	Fiber	
		Terpenoid: sesamin	
		Polyphenols	Hypolipidemic, hypercholesterolemic effects

stomach and liver (al-Turkomani, 1222–1297 CE).

Many Lebanese families have their own recipes that have been passed down from one generation to another. Interestingly, each region of the Middle East has its own style of Za'atar, usually determined by the available local ingredients. In Lebanon, most commonly, a Za'atar blend will include dried leaves of *Origanum syriacum* (normally known as Za'atar), and *Thymbra spicata* (known as wild Za'atar) mixed with *Rhus coriaria* grinded fruits (sumac), toasted sesame seeds, and salt. At home, it is common to mix Za'atar with olive oil to form a spread to be then applied to Lebanese flatbreads "Mankoushe". The detailed composition of Za'atar mixture is shown in Table 2.

Preparation of Mankoushe (Za'atar paste on bread) consists of ½ cup zaatar mixture, ½ cup oil (mostly olive oil), and a round-shape of dough. With a rolling pin, flatten the dough ball until it becomes about ½ cm thick. Meanwhile, mix the Za'atar mixture and oil, then spread it on the dough loaves and gently press using your fingers. Cooked in a heated oven for about 15 to 20 min. Served warm accompanied with homemade labneh cheese (a fresh creamy cheese made from strained yogurt,

**Table 2**

Constituents and amount of Za'atar mixture (Based on different local preparations).

Component	Used part	Range of quantity (Based on local preparation)	Ratio (average)
<b>Za'atar Plants</b>			1
<i>Origanum syriacum</i> (Lebanese thyme)	Dried grinded leaves	1 kg	
70–100%			
<i>Thymbra spicata</i> (Wild thyme)			
0–30%			
<b>Sumac</b> ( <i>Rhus coriaria</i> )	Dried grinded fruits (without seeds)	0.1–0.3 kg	0.2
<b>Sesame</b> ( <i>Sesamum indicum</i> )	Toasted seeds	0.3–0.6 kg	0.5

popular in Lebanon), olives, mint, and a few fresh bites of tomato and cucumber.

The nutritional values of the Za'atar mixture are reported in Table 3.

### 3. Composition of Za'atar: Main bioactive compounds and research findings

As shown in Fig. 1, Za'atar is a mixture containing leaves of *O. syriacum* and *T. spicata*, seeds of sesame, sumac - *R. coriaria* fruits mixed in the percentages reported in Table 2. The following paragraphs discuss the features of the different plants and main components of Za'atar and their chemical composition.

#### 3.1. *Origanum syriacum*

##### 3.1.1. Chemical composition

*Lamiaceae* (formerly known as Labiatae) is a large cosmopolitan botanical family of aromatic plants of mostly shrubs and herbs. It is the largest family of the order of *Lamiales* which includes 236 genera and more than 7,000 species. Many *Lamiaceae* are cultivated as ornamental plants, like ajuga, coleus, and salvia, but other ones are widely used as culinary herbs and spices, such as sage (*Salvia*), thyme (*Thymus*), mint (*Mentha*), oregano or marjoram (*Origanum*), rosemary (*Rosmarinus*), lavender (*Lavandula*), and basil (*Ocimum*) (Khouri, Stien, Eparvier, Ouaini, & El Beyrouthy, 2016a).

The *Lamiaceae* family is found in many parts of the world, but especially in the Mediterranean region (El-Gharbaoui, Benítez, González-Tejero, Molero-Mesa, & Merzouki, 2017). In Lebanon, 136

**Table 3**

Nutritional values of Za'atar mixture. Values refer to 1 tablespoon (10 g), amount per serving.

Content	% Daily Value *
<b>Kcal 28</b>	<b>Kcal from Fat 18</b>
Total Fat 2 g	3%
- Saturated Fat 0 g	0%
- Trans Fat 0 g	0%
- Cholesterol 0 mg	0%
Total Carbohydrates 3 g	1%
- Dietary Fiber 2 g	8%
- Sugars 0 g	0%
Protein 1 g	
Sodium 227 mg	9%
Vitamin A	1%
Vitamin C	1%
Calcium	7%
Iron	11%

\* Percent Daily Values are based on a 2000 calorie diet. Based on Nutritionix Grocery Database (Calories in Zaatar Lebanese Blend from ARZ (nutritionix.com). Values can change slightly depending on local, home-made and traditional receipts.



Fig. 1. Main components of the most common Lebanese Za'atar.

species belonging to 29 genera have been inventoried. Among them, the thyme-like plants *T. spicata* L. and *O. syriacum*, known as Za'atar plants, are widely diffused and the leaves are dried and taken as herbal tea or spices, while other components are employed in food industry for flavoring or as antimicrobial and antifungal agents (El-Gharbaoui et al., 2017; El Beyrouthy, Dhifi, & Arnold-Apostolides, 2013; Khalil et al., 2019). In folk medicine, local people prepare herbal teas from these herbs to relieve headaches, toothaches, colds, asthma, and rheumatism (Gedikoglu, Sökmen, Münevver, Çivit, Ayşe, 2019).

The genus *Origanum* includes about 43 species odour and flavour characteristics of flowers and leaves (Sharifi-Rad et al., 2020), most of them distributed through the eastern Mediterranean region (Tepe, Cakir, & Sihoglu Tepe, 2016). The use of *Origanum* extends to Palaeolithic age (50 000 – 70 000 BCE) (Tepe et al., 2016). The name *Origanum* is originated from two Greek words “oros” (mountain) and “ganos” (joy), referring to the region where the plant is cultivated (Sharifi-Rad et al., 2020). The first written sources were found in Hittite tablets (1600 – 1200 BCE). *Origanum* genus have been propagated by humans over the years for their exclusive culinary and therapeutic properties. In recent years, *Origanum* species growing in Lebanon have gained great commercial importance in local and world markets. Among the different species, *O. syriacum* is preferred because of its high availability and quality (Zgheib et al., 2016). *O. syriacum*, known as Lebanese Za'atar or “zoubaa”, is a perennial (non-wood) and herbaceous plant species which is endemic to a large area of the eastern Mediterranean region especially in Lebanon, Syria, and Palestine (El-Alam et al., 2019). This species was traditionally collected from the wild and used as spicy herb for a long time due to its aroma and flavour to enhance the taste of foods to be then used as a main ingredient of different Za'atar mixture (Alwafa, Mudalal, & Mauriello, 2021). To prevent overexploitation of the plant, the Ministry of Agriculture has regulated its collection (Atallah, El Saliby, Baalbaki, & Talhouk, 2011). Indeed, the Lebanese decree No. 1/340 (1996) only allows the harvest of *O. syriacum* from the first of August till the end of December and recommends the harvesting of the plants without their roots (Zgheib et al., 2016). In addition to its culinary use, dried *Origanum* is mostly used in Lebanese folk medicine against gastrointestinal manifestations including abdominal pain, throat infection, and cough (Shehadeh et al., 2019). The *O. syriacum* extracts contain

different classes of polyphenols including phenolic acids, flavonoids, and phenolic terpenes – with a potent antioxidant and anti-inflammatory activity.

Phytochemical studies on the *O. syriacum* referred mainly to its essential oil and extracts, and showed the dominance of PC, such as carvacrol (CVL) and thymol, which are two monoterpenes phenols present in the essential oil. In addition, rosmarinic acid (RA) is one of the main polyphenols contained not only in *O. syriacum*, but also in other thyme-like plants (Colica, Di Renzo, Aiello, De Lorenzo, & Abenavoli, 2018; Dorman, Bachmayer, Kosar, & Hiltunen, 2004; Petersen, 2003). The chemical structure of RA derives from hydroxycinnamic acid, an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid. RA is a molecule of highly lipophilic and slightly hydrophilic properties, which is usually in the form of a red–orange powder. Solubility of this molecule is higher in most organic solvents. The melting point of RA is 171–175 °C (340–347°F) and the molecular weight is 360.3 g/mol (Alagawany et al., 2017).

In general, the chemical composition of essential oil from the leaves of *O. syriacum* consists of 49.02% monoterpenes, 36.60% oxygenated monoterpenes, and 12.59% sesquiterpenes. The major components are  $\gamma$ -terpinene, CVL, p-cymene, and  $\beta$ -caryophyllene (Alma, Mavi, Yildirim, Digrak, & Hirata, 2003; Al-Kalaldeh, Abu-Dahab, & Afifi, 2010).

### 3.1.2. Experimental studies in cellular and animal models

Studies showed that *O. syriacum* extracts and essential oils exert significant antimicrobial effect (Al Hafi et al., 2016; Assaf, Amro, Mashallah, & Haddadin, 2016). Effects of *O. syriacum* (Table 4) include anti-ulcerogenic property on an *in vivo* prophylactic model (El-Meligy, Awaad, Soliman, Kenawy, & Alqasoumi, 2017) and neuroprotective effect against the glutamate-induced toxicity (Qneibi et al., 2019). Shen et al. utilized a bioactivity-guided fractionation of *O. syriacum* to evaluate the anti-inflammatory activity of fractions and isolated compounds. The anti-inflammatory effects of RA which is the major phenolic compound found in *O. syriacum* has been demonstrated *in vitro* on lipopolysaccharide (LPS)-insulted RAW 264.7 cells where it tuned down the LPS-induction of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) proteins (Shen et al., 2010). RA displays a number of pharmacological and biological activities (Colica et al., 2018) *in vitro*



**Table 4**Main studies *in vitro* and *in vivo* (animal models) with “Za’atar” components.

Component	Models	Model	Treated disorders	Proposed mechanism(s)	References
<i>Origanum syriacum</i> & isolated RA	<i>In vitro</i>	RAW 264.7 cells	Inflammation	↓ LPS-induced iNOS and COX-2 enzymes	(Shen et al., 2010)
Rosmarinic acid	<i>In vitro</i>	Microbiota model	Microbiota modulation	↑ Short-chain fatty acids ↑ PUFA and trans fatty acids metabolic activity ↑ Microbiota growth (e.g. bifidogenic effects)	(Madureira et al., 2016)
	<i>In vitro</i>	Palmitic acid (PA)-exposed HepG2 cells	NASH and liver fibrosis	↑ Antioxidant enzymes Lipid lowering: Activation AMPK	(M. Kim et al., 2020)
	<i>In vivo</i>	db/db mice fed a methionine- and choline-deficient (MCD) diet			
	<i>In vitro</i>	L02 cells exposed to oleic acid	NAFLD	↓ TC, TG, LDL-C, ↓ ALT, AST, MDA ↑ HDL-C, SOD, ATP Downregulation of YAP1, TAZ, and upregulation of PPAR $\gamma$ and PGC-1 $\alpha$	(Luo, Sun, et al., 2020)
	<i>In vivo</i>	HFD Male SD rats			
	<i>In vivo</i>	Estrogen deficiency mature female Wistar rats	Oxidative stress Hyperlipidemia hypercholesterolemia	↓ TC and TG ↑ Antioxidant enzymes	(Zych et al., 2019)
	<i>In vivo</i>	HFD C57BL/6 mice	Obesity NASH	↓ Body weight, TG, TC, and LDL-C	(Seyedan et al., 2016)
	<i>In vivo</i>	Orotic acid induced NAFLD model rats	Hyperlipidemia	↓ TG, TC, FFA Improvement of cell hypertrophy, vacuolation, and cell necrosis in the liver Up-regulation of the phosphorylation of AMPK Inhibition of SREBP-1c	(S.-J. Wang et al., 2019)
<i>Thymbra spicata</i>	<i>In vitro</i>	FFA-induced hepatocyte steatosis (FaO cell line) Human endothelial cell line HECV	Steatosis	↓ Hepatic lipid accumulation ↓ ROS and lipid peroxidation	(Khalil et al., 2019)
	<i>In vivo</i>	HFD-fed mice	NAFLD	↓ Serum cholesterol and TG ↓ MDA	(Akkol et al., 2009; Avci et al., 2006)
CVL	<i>In vitro</i>	3 T3-L1 cell line	Inflammation	Inhibition of inducible COX-2	(Cho et al., 2012)
	<i>In vitro</i>	Caco-2 and HepG2 cell lines	Oxidative stress	Protection against the DNA-damaging effects of H <sub>2</sub> O <sub>2</sub>	(Slamenova et al., 2007)
	<i>In vitro</i>	3 T3-L1 cell line	Obesity	↓ Adipogenic differentiation along with reduction of ChREBP, acetyl-CoA carboxylase- $\alpha$ and $\beta$ expression	(Trajkovic et al., 2018)
	<i>In vivo</i>	Immature female rats	Inflammation	Suppression of inflammatory marker genes	(Mahran et al., 2019)
	<i>In vivo</i>	HFD-fed mice	Obesity	Suppression of bone marrow protein-, fibroblast growth factor 1-, and galanin-mediated signaling ↓ Pro- inflammatory cytokines	(Friedman, 2014)
	<i>In vivo</i>	Rats	Diabetes	Inhibition of NF $\kappa$ B activation of Bax and Bcl-2 protein expression Modulation of Nrf2/HO-1 signalling pathway	(Arkali, Aksakal, & Kaya, 2020)
	<i>In vivo</i>	Chicken Broilers	Microbiota alteration	↑ <i>Lactobacillus</i> spp. ↓ <i>Campylobacter</i> spp.	(Kelly et al., 2017)
	<i>In vivo</i>	Mice	Gut Dysbiosis	↓ Diarrhea ↑ <i>Firmicutes</i> ↓ <i>Proteobacteria</i>	(Mooyottu et al., 2017)
	<i>In vivo</i>	Chicken	Necrotic enteritis	↓ Mortality ↓ Gut lesions ↓ Virulence factors of pathogenic bacteria ↑ Beneficial <i>Lactobacillus</i> spp.	(D. Yin et al., 2017)
	<i>In vivo</i>	Germ-Free Zebrafish	Immunomodulation	↑ Immunostimulation ↓ Pro-Inflammatory markers ↑ Anti-inflammatory markers Microbiota modulation	(Ran et al., 2016)
	<i>In vivo</i>	Chicken Broilers	Intestinal barrier function	↑ Gene expression for intestinal barriers function ↓ <i>Salmonella</i> spp. and <i>Escherichia coli</i> ↓ Sucrase and lactase activity ↑ Intestinal mucosa	(S. Liu et al., 2018)
CVL-thymol	<i>In vivo</i>	Weaning piglets	Intestinal oxidative stress and microbiota imbalance	↓ Intestinal oxidative stress ↓ Pro-Inflammatory cytokines ↑ <i>Lactobacillus</i> spp. ↓ <i>Enterococcus</i> spp.	(Wei et al., 2017)
Sumac - <i>Rhus coriaria</i>	<i>In vivo</i>	Non-insulin-dependent diabetes mellitus (NIDDM) rats	Diabetes	↓ Blood glucose, HbA <sub>1c</sub> , and insulin	(Anwer et al., 2013)
	<i>In vivo</i>	Streptozotocin (STZ)-induced diabetic rats	Diabetes	↓ Blood glucose Balance of TG, TC, HDL-C AND LDL-C levels ↓ AST, ALT, LDH, ALP	(Doğan & Çelik, 2016)

(continued on next page)

Table 4 (continued)

Component	Models	Model	Treated disorders	Proposed mechanism(s)	References
Gallic acid	<i>In vitro</i>	HepG2 and Co-culture hepatocyte-macrophage crosstalk cells	NASH	↓ Fat accumulation via the activation AMPK Amelioration of cell injury and apoptosis ↓ Inflammatory mediator expression Induction of antioxidant enzyme expression	(Tanaka et al., 2020)
	<i>In vivo</i>	HFD male C57BL/6 mice	NAFLD-Obesity	↓ Body weight Protection against hepatic steatosis and insulin resistance Amelioration TG, TC, AAT, ALT ↓ Liver lipid accumulation	(Luque et al., 2014)
	<i>In vivo</i>	Rats	Ulcerative colitis	↑ Probiotic bacteria ↓ Pathogenic bacteria ↓ Bile acid metabolism ↓ Amino acid metabolism	(Li et al., 2019)
Sesame	<i>In vitro</i>	RAW 264.7 cells	Inflammation	↓ Pro-inflammatory cytokines	(Deme et al., 2018)
	<i>In vivo</i>	Rats	Inflammation	↓ Atherosclerotic lesion	(Narasimulu et al., 2018)
	<i>In vivo</i>	Rats	Inflammation	↓ TNF- $\alpha$ , IL-1, IL-6 ↓ ROS, AST, ALT and CRP	(Chiang et al., 2014)
	<i>In vivo</i>	Rats	Inflammation	↑ GSH, GST, GR, CAT, SOD ↓ MDA	(Ahmad et al., 2006)
	<i>In vivo</i>	Rats	Inflammation	↓ MDA ↑ <i>Bacteroides</i> abundance	(Q. Wang et al., 2019)
	<i>In vivo</i>	Birds	Inflammation	↑ <i>Lactobacilli</i> ↓ <i>Escherichia coli</i>	(Salavati et al., 2019)
Olive oil	<i>In vitro</i>	Umbilical vein endothelial cells	Inflammation	↓ Expression of VCAM-1	(Carluccio et al., 2003)
	<i>In vitro</i>	Caco-2 cells	Endothelial dysfunction	↓ Expression of VCAM-1 and E-Selectin	(Catalán et al., 2015)
	<i>In vivo</i>	Rats	Inflammation	↑ <i>Lactobacillus</i> and <i>Clostridium XIVa</i>	(Hidalgo et al., 2017)
	<i>In vivo</i>	Rats	Inflammation	↓ TNF- $\alpha$ , IL-1, IL-6	(Zhuoqun Liu et al., 2019)

Abbreviations: ↓, significantly decreased; ↑, significantly increased; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, (AMP)-activated protein kinase; AST, aspartate aminotransferase; ATP, adenosine triphosphate; CAT, catalase; ChREBP, carbohydrate response element-binding protein; COX-2, cyclooxygenase 2; CRP, C-reactive protein; FFA, free fatty acids; GSH, glutathione; GST, glutathione-S-transferase; GR, glutathione reductase; HbA<sub>1c</sub>, glycated haemoglobin A<sub>1c</sub>; HDL-C, high-density lipoprotein-cholesterol; HFD, High fat diet; IL-1, interleukin 1; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; LDL-C, low-density lipoprotein-cholesterol; LDH, lactate dehydrogenase; MDA, malondialdehyde; NAFLD, Non-alcoholic Fatty Liver Disease; NF $\kappa$ B, nuclear factor kappa B; PA, palmitic acid; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor- $\gamma$  coactivator 1 $\alpha$ ; PPAR $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element binding protein-1c; TAZ, WW-domain-containing transcription regulator 1; TC, total cholesterol; TG, triglycerides; TNF- $\alpha$ , serum levels of tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1; YAP1, yes-associated protein 1.

and *in vivo* with protective and anti-inflammatory effects targeting the activation of nuclear factor kappa-B (NF- $\kappa$ B), resulting in decreased levels of inflammatory mediators (Lin et al., 2017; Luan, Kan, Xu, Lv, & Jiang, 2013). In addition, RA inhibits pancreatic amylase (McCue & Shetty, 2004) and  $\alpha$ -glucosidase (Zhu et al., 2014), and acts on regulating the blood glucose concentration, reducing insulin resistance, and improving  $\beta$ -cell function (Ou, Huang, Zhao, Du, & Wang, 2018). Several reports point to various mechanisms for the protective effect of RA (Elufioye & Habtemariam, 2019), such as a free radical scavenging effect (Adomako-Bonsu, Chan, Pratten, & Fry, 2017), reduction in reactive oxygen species (ROS) generation, and lipid peroxidation (Ghorbani, Sadeghnia, Afshari, & Hosseini, 2019). RA reduces hepatic toxicity and lowers inflammatory mediators, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), oxidized glutathione, lipopolysaccharide (LPS), cytokines, and modulates antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) (Osakabe et al., 2002; Ramalho et al., 2014; Yang, Hong, Lee, Kim, & Lee, 2013).

RA also showed beneficial effects on disease related to the metabolic syndromes, including dyslipidemia, obesity, hypercholesterolemia, and the associated aspects with non-alcoholic fatty liver diseases (NAFLD). The lipid- and cholesterol-lowering effects of RA are well reported (Seyedan, Alshawsh, Alshagha, & Mohamed, 2016; Zych, Kaczmarczyk-Sedlak, Wojnar, & Folwarczna, 2019). Luo et al. (Luo, Sun, et al., 2020) showed that in NAFLD animal model, RA decreased total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL), ALT, AST, and malondialdehyde levels and increased high-density lipoprotein cholesterol (HDL), SOD, and adenosine triphosphate (ATP) levels. In addition, in cultured hepatocytes, RA improved mitochondrial dysfunction and reduced ROS generation and apoptosis that were

stimulated in oleic acid-induced steatosis. In the liver, RA reduces the expression of genes involved in progression of fibrosis and inflammation, both *in vitro* and *in vivo* (El-Lakkany et al., 2017; M. Kim et al., 2020; Lou et al., 2016). In NAFLD models, RA modulated signaling pathways that are attributed to the NAFLD pathogenesis. In details, RA down-regulated YAP1 and TAZ (yes-linked protein1 related to Hippo pathway (Mohagheghi, Khajehahmadi, & Tavilani, 2018)), up-regulated  $\alpha$  peroxisome proliferator-activated receptor gamma and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ) expression that increases the expression of genes involved in gluconeogenesis, fatty acid oxidation, lipid transport, and mitochondrial biogenesis processes (Aharoni-Simon, Hann-Obercyger, Pen, Madar, & Tirosh, 2011). The possible beneficial effects of RA on lipid dysmetabolism can be also attributed to the up-regulation of the phosphorylation of AMPK and to the inhibition of the sterol regulatory element binding protein-1c (SREBP-1c) cracking into the nucleus, following the down-regulation of fatty acid synthesis (S.-J. Wang et al., 2019).

RA and RA-rich medicinal plant extracts revealed a remarkable gastro-protective effect by decreasing oxidative stress, inflammatory response, pro-apoptotic protein expression, and gastric mucosa damage in ethanol-induced gastric injury in mice. RA also showed positive effects on gut microbiota with prebiotic effects. In fact, RA can modulate microbiota increasing the population of diabetes-resistant bacteria and decreasing the amounts of diabetes-sensitive bacteria (Ou et al., 2018). It also increased the gut microbiota diversity by increasing the *Bacteroidetes/Firmicutes* ratio and restoring *Lactobacillus* spp. populations (Wang et al., 2021; K. Wang et al., 2019). Moreover, RA encapsulated with solid-lipid nanoparticles can modulate gut microbiota growth, increases short-chain fatty acid production, and induces polyunsaturated fatty acids (PUFA) and trans fatty acids metabolic activity (Madureira

et al., 2016).

Both *in vitro* and *in vivo* studies reported that RA as one of the major polyphenolic compounds, has health-promoting effects especially with regard to antioxidant and anti-inflammatory capacities, potential probiotic concern, hepatoprotective effects, as well as lipid- and cholesterol-lowering effects. A potential beneficial effect of RA in NAFLD cannot be excluded.

### 3.2. *Thymra spicata*

#### 3.2.1. Chemical composition

*T. spicata* is traditionally used for flavoring different kinds of food products, as herbal tea, and in folk medicine as an antiseptic agent (Golmakani & Rezaei, 2008). *T. spicata* is characterized by a high value of total phenol content (Khalil et al., 2019). Carvacrol (CVL) is very abundant in both essential oils and organic extracts of *T. spicata* ranging from 60 to 70% of total essential oils (Al Hafi et al., 2017; A. Gedikoğlu, Sökmen, & Çivit, 2019). In addition, *T. spicata* is rich in phenolic acids especially RA and flavonoids, mostly luteolin and apigenin in aglycone or glucoside form (Dorman et al., 2004; Khalil et al., 2019).

#### 3.2.2. Experimental studies in cellular and animal models

*T. spicata* might reveal a broad spectrum of biological activities. *In vitro* tests showed that both the essential oils and their chemical constituents, such as thymol and CVL had antimicrobial (A. Gedikoğlu et al., 2019), antioxidant, liver protective, anticoagulation effect, and cholesterol-lowering properties (Bener, 2019; Omar, Abdallah, Barakat, Othman, & Bourinee, 2020). Studies on animal models (Table 4) revealed a potent anti-hypercholesteremic activity for the ethanol extract of *T. spicata* in mice, and antioxidant and anti-steatosis activities in high fatty diet (HFD)-fed mice. In mice, these effects are linked with a decrease in MDA level, as well as in serum cholesterol and triglycerides without inducing any gastric damage (Akkol et al., 2009; Avci, Kupeli, Eryavuz, Yesilada, & Kucukkurt, 2006). *T. spicata* extracts improved the moderate steatosis in NAFLD cellular models by lowering lipid accumulation, oxidative stress, and inflammation (Khalil et al., 2019).

CVL, a naturally synthesized phenolic monoterpene from the mevalonate pathway, is found in many essential oils of the family Labiatae (W.-L. Chen et al., 2015; E. Kim, Choi, Jang, & Park, 2013; Suntres, Coccimiglio, & Alipour, 2014) and is very abundant in both essential oils and organic extracts of *T. spicata* (Khalil et al., 2019). CVL exhibits anti-inflammatory, anti-diabetic, antioxidant, cardioprotective, neuroprotective, and anticarcinogenic properties (Cho, Choi, Park, & Park, 2012). demonstrated that the An *in vitro* study possible anti-inflammatory potential of this compound was due to the inhibition of inducible cyclooxygenase-2 (Cho et al., 2012). An *in vivo* study in rats found that CVL suppresses the expression of inflammatory marker genes such as interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-17 (IL-17), and TNF- $\alpha$  (Mahran et al., 2019).

CVL has a scavenger role for hydrogen peroxide and superoxide radicals. These antioxidant properties of CVL may reduce the free-radical-mediated inactivation of enzyme proteins and thereby maintaining the enzymatic antioxidants activities (Sharifi-Rad et al., 2018). Treatment with CVL has also been shown to protect Caco-2 and HepG2 cells against the DNA-damaging effects of H<sub>2</sub>O<sub>2</sub> (Slamenova, Horvathova, Sramkova, & Marsalkova, 2007).

CVL has been shown to reduce adipogenic differentiation in murine 3 T3-L1 cells along with reduction of autophagy (essential for adipocyte maturation) and of carbohydrate response element-binding protein (ChREBP), acetyl-CoA carboxylase- $\alpha$  and  $\beta$  expression during adipogenic differentiation (Trajkovic et al., 2018). Mice fed a CVL- supplemented diet reduced body weight gain, visceral fat pad weights, and plasma lipid levels, as compared with mice fed a high-fat diet (Friedman, 2014). Inhibition of adipogenesis seems to occur by suppression of bone marrow protein, fibroblast growth factor 1, and galanin-mediated signaling and reduction of the of pro- inflammatory cytokines in

visceral adipose tissues by inhibiting toll-like receptor 2 (TLR2)- and TLR4-mediated signaling (Friedman, 2014). To date, several reports indicated that the pretreatment with CVL ameliorates thioacetamide-induced liver injury in rats. The protective effect of CVL is mediated by the inhibition of NF $\kappa$ B activation pathway and the modulation of Bax and Bcl-2 protein expression, suggesting that the beneficial effect of CVL is associated with the inhibition of inflammation and apoptosis (Nafees et al., 2013). CVL also could have a beneficial effect in the primary prevention of liver cancer, in details, CVL can inhibit human hepatoma HepG2 cell growth by inducing apoptosis by direct activation of the mitochondrial and mitogen-activated protein kinases (MAPK) pathways (Q.-h. Yin et al., 2011).

CVL can protect against gut dysbiosis and modulates gut microbiome composition in animal models (Castañeda-Correa et al., 2018; Kelly et al., 2017). In a mouse model of antibiotic-associated gut dysbiosis and *Clostridium difficile* infection, CVL supplementation significantly reduced the incidence of diarrhea. Apparently, CVL modulated the microbiome composition by increasing the abundance of beneficial bacteria as *Firmicutes*, and significantly reducing the proportion of detrimental flora as *Proteobacteria*, without indicatively affecting the gut microbiome diversity (Mooyottu et al., 2017). Furthermore, CVL increased ileum *Lactobacillus* population and reduced the effect of necrotic enteritis caused by *Clostridium perfringens* in chicken model (D. Yin et al., 2017).

The *in vivo* antioxidant and anti-inflammatory effects of CVL and thymol are likely connected with gut microbiota modulation. Ran et al. (Ran et al., 2016) demonstrated that CVL and thymol might stimulate the immune system by direct interaction with host tissue and by intestinal microbiota modulation in Germ-Free Zebrafish model. The results showed that the immune-relieving effect associated with microbiota alteration was counteracted by the direct effect, leading to the overall immune-stimulating phenotype of CVL and thymol supplementation.

The function of the intestinal barrier and permeability is essential in health maintenance (Bonfrate et al., 2020; Di Palo et al., 2020; P. Portincasa et al., 2020; P. Portincasa et al., 2017; Piero Portincasa et al., 2022).

In the weaning piglet model, supplementation with the CVL-thymol blend restored weaning-induced intestinal oxidative stress and dysfunction of the intestinal barrier. In addition the compound increased *Lactobacillus* genus population and reduced *Escherichia coli* in the jejunum, and decreased the mRNA levels of TNF- $\alpha$ , a pro-inflammatory cytokine (Wei, Xue, Zhou, & Peng, 2017). CVL might provide a positive effect on the intestinal barriers function of broilers by increasing the expression of the occludin, claudin-1, claudin-5, ZO-1 and ZO-2 in intestinal mucosa of small intestine. Interestingly, CVL oral administration reduced the microbial counts of pathogenic bacteria such as *Salmonella* spp. and *Escherichia coli* in the intestines (S. Liu et al., 2018). Taken together, these studies showed that CVL has potent antioxidant, anti-obesity, hepatoprotective effects, and has possible beneficial effect on the modulation of gut microbiota and intestinal barrier.

### 3.3. *Rhus coriaria*

#### 3.3.1. Chemical composition

Sumac - the common name for a genus (*Rhus*) - contains over 250 individual species of flowering plants in the family Anacardiaceae (Rayne & Mazza, 2007). *R. coriaria* L. (Sicilian Sumac) is a wild edible plant growing in the Mediterranean region. It is traditionally used as a table spice for sauce, appetizer, drink, and as a souring agent in food recipes (Alsamri, Athamneh, Pintus, Eid, & Iratni, 2021). *R. coriaria* has an attractive economic importance due to its increasing use in food, cosmetic, and pharmaceutical industries where it is employed for coloring or preservation of foods (Sakhr & El Khatib, 2020). *R. coriaria* is traditionally used as herbal folk medicine in the treatment of stroke, diarrhea, hypertension, diabetes, atherosclerosis, measles, smallpox, and liver disease (Abu-Reidah, Ali-Shtayeh, Jamous, Arráez-Román, & Segura-Carretero, 2015). The fruits are red colored, containing one seed

to be dried, and the ground leaves have been used as a tanning agent due to their high tannin content. *R. coriaria* comprises various substances including phenol acids and flavonoids, such as methyl gallate, kaempferol, and quercetin gallic acid (GA) (Khalil et al., 2021). *R. coriaria* seed composition consists of 11.8% of moisture, 31–48% of carbohydrates, 2.47–4.13% of proteins, which include both 9 essential amino acids (leucine, isoleucine, lysine, phenylalanine, threonine, methionine, valine, tryptophan and histidine with the concentrations of 3.16, 1.79, 2.65, 2.00, 1.57, 0.05, 2.24 and 3.10, and 1.03 mg/g protein, respectively) and 9 non-essential amino acids (arginine, cysteine, aspartic acid, glutamic acid, serine, glycine, alanine, tyrosine, proline at the concentrations of 2.79, 0.10, 3.68, 7.46, 2.26, 2.17, 1.98, 1.27 and 2.26 mg/g protein, respectively). In addition, *R. coriaria* seeds contain 7.51% of lipids, principally oleic acid (C18:1) followed by linoleic acid (C18:2), palmitic acid (C16:0), stearic acid (C18:0), palmitoleic acid (C16:1), linolenic acid (C18:3), and myristic acid (C14:0) at the concentrations of 52.31, 25.57, 16.28, 2.60, 2.11, 0.94, and 0.19 % of the total fatty acids, respectively (Kosar, Bozan, Temelli, & Baser, 2007). *R. coriaria* contains also minerals that are mostly K, Na, Mg, Ca, Fe, Cu, Zn, Mn, P, and vitamins including: thiamin, riboflavin, pyridoxine, nicotinamide, biotin, and ascorbic acid (Kossah, 2009).

The potential therapeutic effects of *R. coriaria* and its bioactive compounds were studied by identifying its antibacterial and antioxidant activities (Thaer, Alawsy, & Al-Jumaily, 2020). The chemical composition of sumac makes it a promising potential food with desirable anti-fibrogenic, antifungal, anti-inflammatory, antimalarial, antimicrobial, antimutagenic, antithrombin, antitumorogenic, oncostatic, antiviral, and neuroprotective bioactivities (Mohamad Khalil, Ali Bazzi, et al., 2020; Pojer, Mattivi, Johnson, & Stockley, 2013; Kubatka et al., 2020).

### 3.3.2. Experimental studies in cellular and animal models

Table 4 summarizes the main studies conducted *in vitro* and *in vivo* using animal models regarding sumac – *R. coriaria*. *R. coriaria* fruits showed antidiabetic properties, as investigated in non-insulin-dependent diabetes mellitus rats, where treatment with *R. coriaria* reduced the levels of blood glucose, glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), and insulin, with a significant improvement in glucose tolerance (Anwer et al., 2013). Dogan & Celik (Doğan & Çelik, 2016) investigated the healing and protective effects of *R. coriaria* against streptozotocin (STZ)-induced diabetic complications in rats. *R. coriaria* supplementation in this model decreased the levels of blood glucose as well as triglyceride and TC. In addition, *R. coriaria* decreased the levels of AST, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatinine, and urea in the diabetic group, showing possible hepato- and renal protective effects. GA, a naturally abundant plant phenolic compound in vegetables and fruits including *R. coriaria*, has shown potent antioxidant and anti-obesity activity with a protective effect on hepatic steatosis in animal models. Daily administration of GA protects against hepatic steatosis, obesity, hypercholesterolemia, and insulin resistance in the HFD-induced NAFLD mice (Luque et al., 2014). In an *in vitro* model of hepatic steatosis, GA attenuated palmitic acid (PA)-induced fat accumulation via the activation of AMPK in HepG2 cells. GA also ameliorated cell viability and suppressed apoptosis-related gene expression and caspase 3/7 activity induced by PA and H<sub>2</sub>O<sub>2</sub> (Tanaka et al., 2020). In addition, GA has been recently reported to attenuate ulcerative colitis and different diseases by modulating the gut microbiota i.e. increasing the number of the probiotic bacteria and inhibiting the growth of pathogenic bacteria (Li et al., 2019).

## 3.4. *Sesamum indicum*

### 3.4.1. Chemical composition

Sesame - *Sesamum indicum* L. is an annual plant belonging to the family of *Pedaliaceae*. Sesame seeds have been used for several thousand years in Eastern, Mediterranean, and African cultures to flavour foods (Prasad Mn, Kr, & S. Prasad, 2012). Nutritionally, sesame seeds are rich

in oil (50–60%) and contains also proteins (18–25%), carbohydrates (13.5%), and ash (5%) (Elleuch, Besbes, Roiseux, Blecker, & Attia, 2007). Specifically, sesame seeds contain high levels of unsaturated fatty acids, mainly oleic (43%) linoleic (35%), palmitic (11%), and stearic acid (7%) which together comprise 96% of the total fatty acids (Saydut, Duz, Kaya, Kafadar, & Hamamci, 2008). Sesame seeds contain also amino acids, mainly methionine, and micronutrients such as lignans (principally sesamol, sesamin, and lignans (Majdalawieh & Mansour, 2019), tocopherol, phytosterol, and minerals. Sesamin, a natural PC, exerts multiple nutritional and health benefits, such as an antihypertensive effect, anticholesterolemic, lipid-lowering, and anticancer activities (Elleuch, Bedigian, & Zitoun, 2011).

In addition, peptides from sesame seed have demonstrated multifunctional proprieties as antioxidative and antihypertensive agents (Aondona et al., 2021). Regarding minerals, the highest is calcium (960 mg/100 g), followed in descending order by phosphorus (659 mg/100 g), potassium (582 mg/100 g), magnesium (362 mg/100 g), iron (19.2 mg/100 g), and sodium (12 mg/100 g) (Prasad Mn et al., 2012).

### 3.4.2. Experimental studies in cellular and animal models

Beneficial effects of sesame have been reported (Table 4). *In vitro*, sesame oil shows anti-inflammatory properties in monocyte derived macrophages/RAW 264.7 macrophages (Deme, Narasimhulu, & Parthasarathy, 2018). Potent anti-inflammatory and anti-atherosclerotic properties of sesame are also linked with the expression of pro-inflammatory cytokines, as reported after treatment with LPS (100 ng/ml). This effect was also tested *in vivo*, in mice. In this animal model, feeding mice with sesame oil and its aqueous extract for 3 months, significantly reduced atherosclerotic lesion; by inducing the expression of genes involved in cholesterol metabolism (Narasimhulu, Riad, & Parthasarathy, 2018). There are different mechanisms related to the antioxidant effects of sesame components, as depicted in Fig. 2. In rat models of liver injury, sesame administration reduced the oxidative stress as indicated by the reduction of classical markers of inflammation and the increase of antioxidant markers. The serum levels of cytokines such as TNF- $\alpha$ , interleukin (IL)-1, IL-6, as well as of ROS and AST, ALT, and C-reactive protein (CRP) were reduced in rats fed with sesame (Chiang et al., 2014). Also, the antioxidant effects of sesame seems to be depending on the stimulation of the enzymatic and nonenzymatic antioxidants (Ahmad et al., 2006). Ahmad et al. (Ahmad et al., 2006) studied the effect of sesame oil on rats with middle cerebral artery occlusion - induced cerebral ischemia injury. They highlighted the neuroprotective effects of diet enriched with sesame oil for 15 days, which seemed to stimulate the antioxidant defence through an increase in glutathione, glutathione-S-transferase, glutathione peroxidase (GPX), glutathione reductase (GR), CAT, SOD and TBARS), and a reduction in lipid peroxidation.

In addition, sesame lignans, in particular sesamin, might improve the gut microbiota profile. In a recent *in vivo* study on rats, Wang et al. (Q. Wang et al., 2019) reported that consumption of sesamin (50 mg/day) for 2 weeks not only alleviated stress-induced gut barrier integrity damage, but also enhanced the relative abundance of *Bacteroides* and S24-7 by reducing lipopolysaccharide levels. Sesame is considered a probiotic supplementation because of its bioactive peptides. In birds model, sesame intake decreased the viable cell count of *Escherichia coli* and increased the population of lactobacilli (Salavati, Rezaei-pour, Abdullahpour, & Mousavi, 2019).

## 3.5. Olive oil

### 3.5.1. Chemical composition

Olive oil is a natural juice obtained by mechanical or other physical means - under conditions that do not cause any changes in the oil - from the fruit of the olive tree (*Olea europaea* L.). Most of the world's olive trees grow in the Mediterranean Basin. Olive oil is a major component of the diet in countries surrounding the Mediterranean sea, but in the past



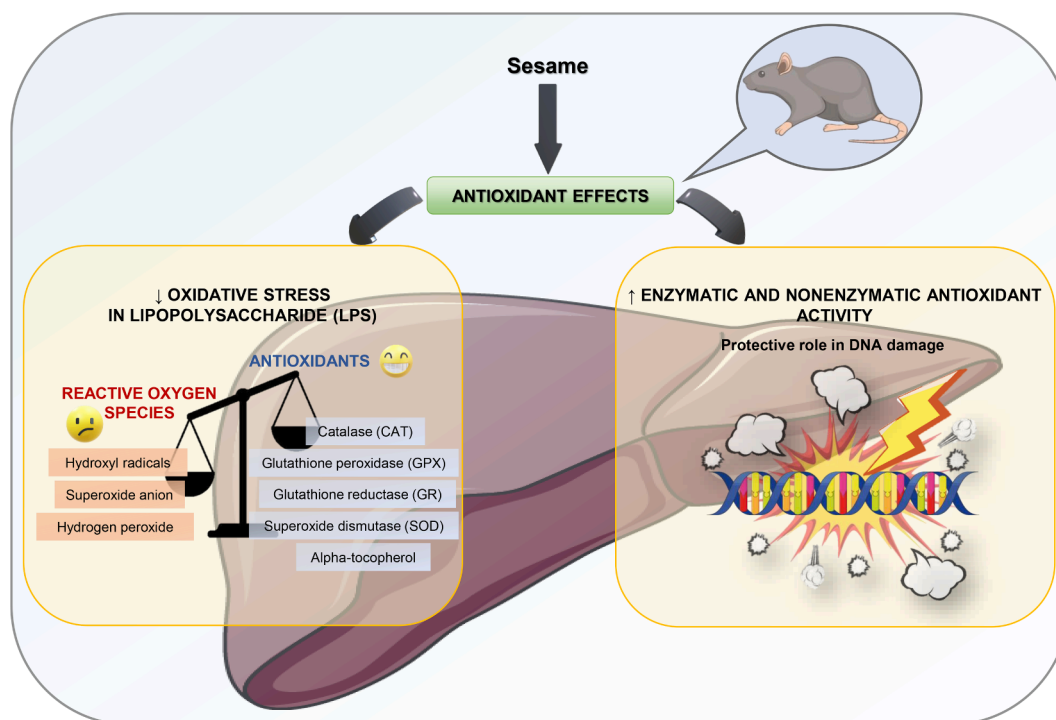


Fig. 2. Antioxidant activity of sesame. Abbreviations: ↓, significantly decreased; ↑, significantly increased.

years, this oil has become more popular among consumers in Northern Europe, the United States, Canada, and Australia (Apostolos Kiritsakis, Turkan, & Kiritsakis, 2020). Olive oil is primarily a mixture of triacylglycerols (~99%). In addition, olive oil contains free fatty acids, mono- and diacylglycerols, and an array of lipids such as hydrocarbons, sterols, aliphatic alcohols, tocopherols, and pigments. The content of free fatty acid depends on the type of olive oil (i.e., extra virgin olive oil, virgin olive oil, olive oil, etc) and it is considered one of its quality parameters. Fatty acids present in olive oil ranges from 55 to 85% oleic acid (C18:1), 7.5–20% palmitic acid (C16:0), 7.5–20% linoleic acid (C18:2), 0.5–5% stearic acid (C18:0), 0.3–3.5% palmitoleic acid (C16:1), and 0.0–1.5% linolenic acid (C18:3). Myristic, heptadecanoic, and eicosanoic acids are found in trace amounts (A. Kiritsakis & Markakis, 1988). In addition, olive oil contains a number of bioactive compounds such as polyphenols that are strong antioxidants and radical scavengers and inhibit low-density lipoprotein (LDL) oxidation (George et al., 2018); where the major PC in olive oil are oleuropein, hydroxytyrosol, and tyrosol, which have been focused on throughout many studies to investigate their biological properties (Tuck & Hayball, 2002).

### 3.5.2. Experimental studies in cellular and animal models

The PC contained in olive oil exert anti-inflammatory effects through different mechanisms such as the antioxidant activity is exerted by causing several modifications in the signaling cascade and transcription network, and decrease of the adhesion of immune cells (Tangney & Rasmussen, 2013). Table 4 summarized the main features of different studies. In human umbilical vein endothelial cells cultured *in vitro*, Carluccio et al. studied the antioxidant activity of olive oil polyphenols. After incubation with LPS or cytokines, polyphenols reduced the endothelial activation and expression of vascular cell adhesion molecule-1 (VCAM-1) (Carluccio et al., 2003). As verified by Catalán et al., olive oil is able to protect against endothelial dysfunction. Briefly, when Caco-2 cells were treated with olive oil polyphenols, reduction in the biomarkers of endothelial dysfunction such as VCAM-1, E and P-Selectin was pronounced (Catalán et al., 2015). In addition, PC extracted from olive pomace (PEOP) protected hepatocytes and endothelial cells against triglyceride accumulation and oxidative stress, in details, PEOP

extract ameliorated hepatic lipid accumulation and lipid-dependent oxidative imbalance by modulation of the expression of peroxisome proliferator-activated receptors (PPARs) and of stearoyl-CoA desaturase 1 (SCD-1) in hepatic cells and intercellular adhesion molecule-1 (ICAM-1), NF- $\kappa$ B in endothelial cells (Vergani et al., 2017).

Animal studies showed an association between olive oil consumption, and gut microbiota. Rats fed with extra virgin olive oil (EVOO) for 12 weeks improved the composition of gut microbiota. After EVOO consumption the abundances of *Lactobacillus* and *Clostridium XIVa* were significantly higher compared to control group (Hidalgo et al., 2017). The genus *Clostridium XIVa* – one of the main strict anaerobic groups in the intestine – has a pivotal role in reduction of TC and anti-inflammatory activity by means the production of butyrate and the short chain fatty acid (Deiana, Serra, & Corona, 2018). EVOO consumption also influenced the *Bacteroidetes/Firmicutes* ratio in 26 mice fed for 12 weeks (Gonzalez-Bulnes et al., 2018). Similar findings were obtained when mice fed for 8 weeks with hydroxytyrosol – a phenolic compound of EVOO (Zhuoqun Liu, Wang, Ma, & Wen, 2019).

The results of this study showed an improvement of inflammation levels resulting in a reduction of TLR-4, TNF- $\alpha$ , IL-1 $\beta$ , IL-6. Moreover, an increasing in *Bacteroides* and a reduction of *Proteobacteria* and *Deferribacteres* in gut microbiota were found.

## 4. Clinical studies

Despite the clear evidence from cellular and animal studies, well-established human studies are necessary to support the health-promoting and preventive effects of herbs, food ingredients and functional foods. Randomized clinical trials (RCT) investigating the bioactivity of foods are complex as they imply limitations due to methodological, food-related and host-related factors. A main critical problem encounters the clinical medicine is summarized in understanding the ultimate translational value of basic studies, when beneficial effects are anticipated on human health. Main problems pend on cellular, animal models employed, dose–effect findings, rue application in humans, as well as the additive effect of combined components of different functional foods, are not totally known. Here, we try to discuss

the most important clinical evidence of beneficial effects of Za'tar components and major bioactive compounds.

#### 4.1. *Origanum syriacum*

Despite the diffused use of *O. syriacum*, the main component of mixed Za'atra, in food and herbal medicine, and the accumulating scientific-based evidence of its bioactivity, no clinical studies on humans after *O. syriacum* intake are present in the literature. Nevertheless, the effects of different PC present in *O. syriacum* have been reported. Human studies of RA – the main PC of *O. syriacum* – in humans, appear in Table 5. RA acts as anti-inflammatory PC in cellular and/or animal models (suggesting the potential of RA in treating inflammatory diseases through multiple mechanisms (Luo, Zou, et al., 2020)). Some anti-inflammatory effects of RA might be evident also in humans. The effect of RA on atopic dermatitis, an inflammatory skin disorders was evaluated by Lee et al., 2008, the study showed that the erythema on antecubital fossa and the transepidermal water loss was significantly reduced at 4 and 8 weeks after RA application to the elbow flexures (Lee, Jung, Koh, Kim, & Park, 2008). RA- rich *Rosmarinus officinalis* extract showed promising results in the treatment of resistant asthma in a randomized, double-blind, active-comparator study to be then conducted on asthmatic patients resistant to routine treatment (Osakabe et al., 2004). In addition, RA and RA- enriched *Perilla frutescens* extract exerted anti-inflammatory and anti-allergic effects in seasonal allergic rhino conjunctivitis patients in which their symptoms were daily recorded and the profiles of infiltrating cells and concentration of cytokines were measured in nasal lavage fluid. RA supplementation resulted in a significant decrease in symptoms rate. RA also significantly decreased the numbers of neutrophils and eosinophils in nasal lavage fluid (Takano et al., 2016). Connelly et al., (Connelly et al., 2014) showed that high-RA spearmint tea alleviates osteoarthritis symptoms, in a randomized, double-blind study, and the daily consumption of high-RA spearmint tea for 4 months by participants with knee osteoarthritis showed a significant improvements in pain scores and physical function. Randomized controlled trials (RCT) investigating the safety profile of RA and RA-rich extracts are recently reported. In details, single dose of *Melissa officinalis* extract containing 500 mg of RA appears to be safe and tolerable in healthy individuals. Moreover, food intake increased the exposure of RA and delayed its absorption (Noguchi-Shinohara et al., 2015). In addition, a recent randomized placebo-controlled double-blind 24-week trial using RA-rich *Melissa officinalis* extract on patients with mild dementia due to Alzheimer's disease showed that 500 mg of RA taken daily was safe and well-tolerated by patients and improved Alzheimer's disease -related neuropsychiatric symptoms. (Noguchi-Shinohara et al., 2020).

#### 4.2. *Thymra spicata*

Although the recently growing interest in discovering the bioactivity of *T. spicata*, there are no clinical studies on humans. However, *T. spicata* contains a panel of PC that have been tested as single compounds, such as Carvacrol and rosmarinic acid. Table 5 depicts the effect of CVL, the main polyphenol compound of *T. spicata*, in humans. CVL has been approved as a food additive by the FDA and it was involved in the list of chemical flavourings by the Council of Europe (De Vincenzi, Stamatii, De Vincenzi, & Silano, 2004). Besides, many clinical evidence reported the potential therapeutic effects of CVL in humans. A randomized, placebo-controlled trial (Mohammad Reza Khazdair & Boskabady, 2019) showed that CVL treatment of veterans exposed to sulphur mustard increased the forced expiratory volume-one second (FEV1), reduced the respiratory symptoms (chest wheeze, cough and wheeze), reduced the inflammatory mediators such as TNF- $\alpha$ , epidermal growth factor, vascular endothelial growth factor, monocyte chemoattractant protein-1, and ameliorated the haematological parameters, oxidant/antioxidant biomarkers and pulmonary function (M. R. Khazdair, Alavinezhad, & Boskabady, 2018). In asthmatic patients, CVL

supplementation increased the pulmonary function and decreased each of the respiratory symptoms, inflammatory cells, and high-sensitivity C-reactive protein (hs-CRP) in asthmatic patients (Alavinezhad, Khazdair, & Boskabady, 2018). Recently, Ghorani et al., investigated the pulmonary function, oxidant/antioxidant parameters and cytokine levels in asthmatic patients after CVL capsules supplementation by randomized, double-blind, clinical trial (Ghorani, Alavinezhad, Rajabi, & Boskabady, 2021). Respiratory symptoms were significantly increased after one and two months of CVL supplementation, in addition, oxidative markers such as nitrite, malondialdehyde (MDA), superoxide dismutase (SOD), thiol and catalase (CAT) as well as the level of inflammatory cytokines (IL-4, IL-10 and IFN- $\gamma$ ) in serum and supernatant of peripheral blood mononuclear cells were significantly improved.

#### 4.3. *Rhus coriaria*

Due to the fact that the therapeutic potential of sumac has been studied and evaluated in scientific circles including *in vitro* and *in vivo* studies, Sumac has also reached the stage of clinical trials in humans and much attention have been paid to the hepato- and cardioprotective effects of *R. coriaria* (Anwar, Samaha, Baydoun, Iratni, & Eid, 2018; Pourahmad, Eskandari, Shakibaei, & Kamalinejad, 2010). In this regard, the lipid-lowering, antidiabetic and anti-inflammation effects of *R. coriaria* have been investigated in different human studies (Table 5). Hajmohammadi et al. using a two-arm, double-blind placebo-controlled randomized clinical trial, showed that *R. coriaria* supplementation led to a significant increase in high-density lipoprotein-cholesterol (HDL-C) and apolipoprotein-A1 levels in patients with hyperlipidemia (Hajmohammadi et al., 2018). Asgary et al. investigated the beneficial effect of sumac capsules on vascular function and cardiovascular risk factors. After sumac consumption, they observed an improvement on measures of endothelial vasodilator function. In addition, a significant reduction in blood pressure, serum TC and low-density lipoprotein-cholesterol (LDL-C), non-HDL-C, and body mass index (BMI) was observed in the sumac group compared to the placebo group (Asgary et al., 2018). Sabzghabaei et al. investigated the clinical effects of sumac fruits on dyslipidemia in 12–18 years-old adolescents using randomized triple-blinded clinical trial, and after one month trial, *R. coriaria* reduced the serum levels of TC, LDL-C, and TG (Sabzghabaei, Kelishadi, Golshiri, Ghannadi, & Badri, 2014). In a recent study, Kazemi et al. assessed the effects of sumac powder supplementation on hepatic fibrosis and some metabolic markers in patients with NAFLD using a randomized double-blind placebo-controlled clinical trial. After 12-weeks of supplementation, subjects in the sumac group showed a decrease in hepatic fibrosis and liver enzymes as well as fasting blood sugar, serum insulin, HbA<sub>1c</sub>, insulin resistance index, LPO, and C-reactive protein compared to the placebo (Kazemi et al., 2020). These findings show that *R. coriaria* has a wide spectrum of effects on NAFLD and related diseases. Effects might depend on diverse bioactive polyphenolic compounds including GA, methyl gallate, and flavonoids such as quercetin, isoquercetin, kaempferol, and myricetin-3-O- $\alpha$ -L-rhamnoside. These substances that are reported as the main constituents in this plant, are well recognized for their antioxidant, anti-inflammatory and hepatoprotective activities.

#### 4.4. *Sesamum indicum*

Several *in vivo* human studies investigated the dose/effect relationship of these compounds on metabolic diseases in different populations, namely hypertensive, hyperlipidemic, hypercholesterolemic, type 2 diabetes, overweight or obese subjects, subjects with rheumatoid arthritis, and healthy individuals. Table 5 listed the main clinical controlled trials involving the intake of sesame. Sesame seed and its oil were used against several diseases including increased blood pressure, LPO, and oxidative stress. In addition, sesame had also a positive effects on osteoarthritis (OA), as reported by Sadat et al. (Eftekhari Sadat et al., 2013). They evaluated the effects of sesame seeds intake (40 g/day) for

**Table 5**  
Main clinical controlled trials involving intake of “Za’atar” components.

Component	Sample Size	Gender (Age)	Participants	Format, dose	Duration of study	Action	References
<b>RA &amp; RA-rich extracts</b>	N = 23	Men and women (18–87 years)	Seasonal allergic rhinoconjunctivitis subjects	RA-rich herbal extract (50 or 200 mg/day)	30 days	↓ Asthma symptoms	(Osakabe et al., 2004)
	N = 30	Men and women (21–53 years)	Seasonal allergic rhinoconjunctivitis subjects	RA-rich herbal extract (50 and 200 mg/day)	21 days	↓ Neutrophils and eosinophils numbers ↓ Allergic symptoms	(Takano et al., 2016)
	N = 46	Men and women (greater than 18 years)	Knee osteoarthritis subjects	RA (~280 mg/day)	16 weeks	↓ Pain ↓ Knee osteoarthritis symptoms ↑ Physical function	(Connelly et al., 2014)
<b>CVL</b>	N = 21	Men and women (median age 53.36 ± 4.77 years)	Sulphur mustard-induced subjects	CVL (1.2 mg/kg/day)	60 days	↓ Respiratory symptoms and inflammatory mediators ↑ Pulmonary function and antioxidant parameters	(Mohammad Reza Khazdair & Boskabady, 2019)
	N = 25	Men and women (27–30 years)	Sulphur mustard-induced subjects	CVL (1.2 mg/kg/day)	2 months	↓ Inflammatory cells and oxidant biomarkers	(M. R. Khazdair et al., 2018)
	23	Men and women (20–70 years)	Asthmatic subjects	CVL (1.2 mg/kg/day)	2 months	↓ Respiratory symptoms and total and differential white blood cell ↓ hs-CRP	(Alavinezhad et al., 2018)
<b>Sumac – Rhus coriaria</b>	N = 80	Men and women (20–65 years)	Hyperlipidemic subjects	Sumac capsule (500 mg/ twice per day)	42 days	↓ HDL-C ↓ Apolipoprotein-A1	(Hajmohammadi et al., 2018)
	N = 30	Men and women (35–65 years)	Hyperlipidemic subjects	Sumac capsule (500 mg/ twice per day)	28 days	↓ BMI, systolic and diastolic blood pressure, TC and LDL-C ↑ FMD	(Asgary et al., 2018)
	N = 72	Men and women (12–18 years)	Obese subjects	Sumac capsule (500 mg/ three time/day)	28 days	↓ TC, LDL-C and TG	(Sabzghabae et al., 2014)
	N = 84	Men and women (20–60 years)	Non-alcoholic fatty liver subjects	Sumac (2000 mg/day)	84 days	↓ Hepatic fibrosis, liver enzymes ALT & AST ↓ FBS, HbA <sub>1c</sub> , HOMA-IR, MDA, hs-CRP ↑ QUICKI	(Kazemi et al., 2020)
<b>Sesame</b>	N = 40	Men and women (45–65 years)	Hypertensive diabetics subjects	Oil (35 g/day)	45 days	↓ Systolic and diastolic blood pressure ↓ Plasma glucose, HbA <sub>1c</sub> , TC, LDL-C, and TG ↓ TBARS levels ↑ Activities of enzymic and the levels of nonenzymic antioxidants	(D. Sankar et al., 2006)
	N = 30	Men (median age 52.7 ± 10.4 years)	Hypertensive subjects	Oil (35 g/day)	60 days	↑ FMD ↓ ICAM levels	(Karatzi et al., 2012)
	N = 21	Men and women (median age 50.9 ± 3.7 years)	Hyperlipidemic subjects	Seeds (40 g/day)	4 weeks	↓ TC and LDL-C ↑ Time for erythrocyte hemolysis and the lag phase of LDL oxidation ↓ TBARS levels	(P. R. Chen et al., 2005)
	N = 38	Men and women (50–70 years)	Hyperlipidemic subjects	Seeds (40 g/day)	60 days	↓ TBARS levels ↑ GPX and SOD ↓ TC and LDL-C	(Alipoor et al., 2012)
	N = 60	Men and women (median age 58 ± 3 years)	Type 2 diabetes subjects	Oil (35 g/day)	60 days	↓ TC, LDL-C and TG levels ↑ HDL-C ↑ Activities of enzymic and the levels of nonenzymic antioxidants	(Devarajan Sankar et al., 2011)
	N = 41	Men and women (18–60 years)	Type 2 diabetes subjects	Seeds (28 g/day)	6 weeks	↓ TC, LDL-C and AIP	(Mirmiran et al., 2013)
	N = 50	Men and women (50–70 years)	Osteoarthritis subjects	Seeds (40 g/day)	60 days	↑ KOOS Questionnaire ↓ TUG Questionnaire	(Eftekhari Sadat et al., 2013)
	N = 44	Women (median age 55.49 ± 5.98 years)	Subjects with rheumatoid arthritis	Sesamin (200 mg/day)	6 weeks	↓ Serum levels of MDA ↑ TAC and HDL-C levels ↓ Weight, BMI, waist-to-hip ratio, body fat, systolic blood pressure, TG, TC, and LDL-C	(Helli et al., 2015)
	N = 13	Women (median age 27.6 ± 6.5 years)	Healthy subjects	Oil (22.5 g/day)	4 weeks	↑ Serum γ-tocopherol concentrations ↓ α-/γ-tocopherol ratios	(Lemcke-Norojärvi et al., 2001)
	N = 26	Postmenopausal women	Healthy subjects	Seeds (50 g/day)	5 weeks	↓ TC, LDL-C, the ratio of LDL-C to HDL-C, TBARS in LDL, and serum dehydroepiandrosterone sulphate ↑ α-/γ-tocopherol ratios ↑ SHBG and 2-OHE <sub>1</sub>	(Wu et al., 2006)
<b>Olive oil</b>	N = 24	Men (median age 69.9 ± 2.1 years)	Peripheral vascular disease subjects	Oil (n.a.)	9 months	↓ TC, LDL-C ↓ TG concentrations	(Ramirez-Tortosa et al., 1999)

(continued on next page)

Table 5 (continued)

Component	Sample Size	Gender (Age)	Participants	Format, dose	Duration of study	Action	References
	N = 171	Men and women (age < 80 years)	Hypertensive and diabetes subjects	Oil (24.9 g/days)	n.a.	↓ Risk of a first myocardial infarction	(Fernandez-Jarne, 2002)
	N = 62	Men and women (median age 84 ± 7.4 years)	Normotensive and hypertensive subjects	Oil (60 ml/days)	4 weeks	↓ TC and LDL-C	(Perona, 2004)
	N = 24	Women (24–27 years)	Hypertensive subjects	Oil (60 ml/day) with or without polyphenol-rich (~30 mg/da)	2 months	↓ Systolic and diastolic blood pressure	(Moreno-Luna et al., 2012)
	N = 21	Men and women (53–68 years)	Hypercholesterolemic subjects	Oil (40 ml) with high (400 ppm) or low (80 ppm) content in PC	2 h	↑ Endothelial function and NO <sub>(x)</sub> ↑ LPO and 8-epi prostaglandin-F2α	(Ruano et al., 2005)
	N = 40	Men (median age 67 ± 8.7 years)	Coronary heart disease subjects	Oil (50 ml/days)	3 weeks	↓ Plasma oxidized LDL and lipid peroxide levels ↑ GPX ↓ Systolic blood pressure	(Fitó et al., 2005)
	N = 100	Men and women (median age 64 ± 6 years)	Subjects with high cardiovascular risk	Oil (1 l/week)	3 years	↓ Urine 12-HETE/creatinine ↓ NAFLD	(Pintó et al., 2019)
	N = 66	Men and women (median age 46.3 ± 13.6 years)	Non-alcoholic fatty liver subjects	Oil (20 g/days)	12 weeks	↓ Fatty liver grade, weight, waist circumference, and blood pressure ↓ AST ↓ Serum triacylglycerols and fat mass	(Rezaei et al., 2019)
	N = 30	Men (41–56 years)	Healthy subjects	Oil	8 weeks	↓ ICAM-1	(Yaqoob et al., 1998)
	N = 6	Men (27–33 years)	Healthy subjects	Oil (50 g/day)	24 h	↓ Urinary excretion of 8-iso-PGF <sub>2α</sub>	(Visioli et al., 2000)
	N = 12	Men (20–22 years)	Healthy subjects	Oil (25 ml/days)	4 days	↓ Plasma oxidized LDL, 8-oxo-dG and MDA ↑ HDL-C and GPX	(Weinbrenner et al., 2004)
	N = 10	Women (47–67 years)	Healthy subjects	Oil (50 ml/days)	8 weeks	↓ DNA damage	(Salvini et al., 2007)

Abbreviations: ↓, significantly decreased; ↑, significantly increased; AIP, atherogenic index plasma; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; FBS, fasting blood sugar; FMD, flow-mediated dilatation; GPX, glutathione peroxidase; HbA<sub>1c</sub>, glycated haemoglobin A<sub>1c</sub>; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; ICAM, intracellular adhesion molecule; ICAM-1, intracellular adhesion molecule 1; KOOS, knee injury and osteoarthritis outcome score; LDL-C, low-density lipoprotein-cholesterol; LPO, lipoperoxides; MDA, malondialdehyde; NAFLD, Non-alcoholic Fatty Liver Disease; NO<sub>(x)</sub>, nitrates/nitrites; PC, phenolic compounds; QUICKI, quantitative insulin sensitivity check index; SHBG, serum sex hormone-binding globulin; SOD, superoxide dismutase; TAC, total antioxidant capacity; TBARS, thiobarbituric acid-reactive substances; TC, total cholesterol; TG, triglycerides; TUG, timed up and go; Urine 12-HETE/creatinine, urine 12(S)-hydroxyeicosatetraenoic acid/creatinine; 2-OHE<sub>1</sub>, urinary 2-hydroxyestrone; 8-epi prostaglandin-F2α, 8-epi-F2α-8-epi prostaglandin-F2α; 8-oxo-dG, 8-Oxo-2'-deoxyguanosine.

60 days in 50 men and women with OA by clinical assessments (knee injury and osteoarthritis outcome score (KOOS) and timed up and go (TUG) tests). Results showed an increase of KOOS Questionnaire and decrease of TUG Questionnaire resulting in a positive correlation between OA and sesame consumption. One of important factor that has role in OA is oxidative stress. The results of a clinical trial conducted by Sankar *et al.* (D. Sankar, Rao, Sambandam, & Pugalendi, 2006) highlighted that the consumption of sesame oil by 40 hypertensive diabetics patients (22 males and 18 women, aged 45–65 years) improved the antioxidant status by increasing activities of enzymatic and the levels of nonenzymatic antioxidants – and improved lipid profiles – by reducing TC, LDL-C, TG and increasing HDL-C. Similar findings were obtained in a further study conducted by Sankar *et al.* (Devarajan Sankar, Ali, Sambandam, & Rao, 2011) on 60 type 2 diabetes patients fed for 60 days with sesame oil (35 g/day). Sesame decreased TC, LDL-C, and TG levels and increased HDL-C; in addition, increased activities of enzymatic and the levels of nonenzymatic antioxidants were observed.

Moreover, sesame oil consumption (35 g/day for 60 days) revealed a beneficial effect on endothelial function of 30 hypertensive men (Karatzi *et al.*, 2012). The results underlined that intracellular adhesion molecule (ICAM) decreased significantly after 60 days and flow-mediated dilatation (FMD) increased significantly after 2 h sesame consumption compared with baseline.

In hyperlipidemic subjects, sesame seeds consumption (40 g/day) for 4 weeks improved the lipid profile by a reduction in TC and LDL-C by

6.4% and 9.5% respectively, as reported by Chen *et al.* (P. R. Chen *et al.*, 2005). Additionally, sesame seeds decreased the level of thiobarbituric acid reactive substances (TBARS) by 19.3% and increased the erythrocyte hemolysis time by 3.2% after 4 weeks. This means that sesame can boost antioxidant capacity in hyperlipidemic patients.

Alipoor *et al.* (Alipoor, Haghighian, Sadat, & Asghari, 2012) studied the effects of a daily intake of 40 g of sesame seeds for 60 days in 38 hyperlipidemic patients - ranged between 50 and 70 years. The results of this study highlighted a significant reduction in TC and LDL-C. Moreover, sesame seeds reduced the LPO measured by the formation of TBARS, which measures malondialdehyde (MDA) - a marker for oxidative stress, and increased the antioxidative enzyme, such as GPX, SOD. These results suggested a positive correlation between sesame intake and antioxidant effect by inhibit LPO.

Similar results were found by Helli *et al.* in a randomized, double-blind, placebo-controlled clinical trial (Helli, Mowla, Mohammadshahi, & Jalali, 2015). In this study they evaluated the lipid profiles and the antioxidant capacity after intake of sesame (200 mg/day sesamine) for 6 weeks in 44 women with rheumatoid arthritis. Compared to the control group, the sesamine group significantly decreased weight, BMI, TG, TC, and LDL-C. Additionally, it increased total antioxidant capacity (TAC) and HDL-C levels and decreased MDA levels. Therefore, constituents from sesame - sesamine in particular - had protective effects against oxidative stress.

Sesame has positive effects on CVD risk factors in type 2 diabetics



patients (Mirmiran, Bahadoran, Golzarand, Rajab, & Azizi, 2013). This study assessed the intake of 28 g/day of sesame seeds for 6 weeks in 41 subjects, resulting in a decrease of TC, LDL-C, and atherogenic index of plasma (AIP).

The effects of sesame were studied not only on subjects with metabolic diseases, but also on healthy subjects. The intake of sesame oil (22.5 g/day) for 4 weeks in 13 women increased serum  $\gamma$ -tocopherol concentrations (Lemcke-Norojarvi et al., 2001). Another study on healthy postmenopausal women was conducted by Wu et al. (Wu, Kang, Wang, Jou, & Wang, 2006) where they assessed that the intake of 50 g/day of sesame seeds for 5 weeks decreased TC, LDL-C, the ratio of LDL-C to HDL-C, TBARS in LDL-C, and increased  $\alpha$ -/ $\gamma$ -tocopherol ratios. These results indicate that sesame consumption benefits healthy subjects by improving both lipid profiles and antioxidant status.

#### 4.5. Olive oil

Olive oil, in particular EVOO, has raised much attention in research due to its richness in beneficial substances for human health (Table 5). Since 1999, researchers have investigated the effects of EVOO consumption in comparison to refined olive oil on subjects with peripheral vascular disease (Ramirez-Tortosa et al., 1999). Twenty-four men consuming EVOO for 9 months showed a decrease in TC, LDL-C, and TG levels. This suggests that antioxidants present in EVOO protect LDL against oxidation more than refined olive oil. Similar findings were obtained by Perona et al., who studied the daily intake of virgin olive oil (VOO) in normotensive and hypertensive men and women (Perona, 2004). VOO consumption (60 ml) for 4 weeks decreased TC and LDL-C in normotensive subjects but had no effect on hypertensive subjects. In another study, 24.9 g/day of olive oil reduced the risk of a first myocardial infarction in 171 hypertensive subjects (Fernandez-Jarne, 2002).

Most of the positive effects of olive oil are attributed to its minor components, such as polyphenols. In this regard, Moreno-Luna et al. (Moreno-Luna et al., 2012) evaluated the effects of polyphenols on human health. Two different diets were administered by 24 hypertensive young women for 2 months: one with polyphenol-rich (~30 mg/day) olive oil (60 ml/day) and another one with polyphenol-free olive oil (60 ml/day). Results showed that polyphenol-rich olive oil decreased by 7.91 mm Hg the systolic and by 6.65 mm Hg the diastolic blood pressure.

Ruano et al. (Ruano et al., 2005) assessed that EVOO - rich in PC - improves endothelium-dependent microvascular vasodilatation during the first 4hrs of the postprandial period in patients with hypercholesterolemia. In addition, EVOO intake produces a greater increase in concentrations of nitrates/nitrites ( $\text{NO}_{(\text{x})}$ ) and a lower increase in LPO and 8-epi prostaglandin- $\text{F}_{2\alpha}$ . Fitó et al. (Fitó et al., 2005) showed that, in men with coronary heart disease, the daily consumption of virgin olive oil (50 ml/days) for 3 weeks decreased systolic blood pressure and oxidative stress, as compared with refined olive oil.

EVOO consumption is also able to reduce the prevalence of NAFLD in subjects with high cardiovascular risk (Pintó et al., 2019). In this recent study, one hundred participants were divided into three different treatments for 3 years: diet + EVOO consumption, diet + nuts consumption, and a control diet in order to explore the effects of EVOO diseases. The results highlighted that EVOO consumption reduced NAFLD and urine 12(S)-hydroxyeicosatetraenoic acid/creatinine concentration and that was positively correlated with improvement in insulin resistance. In another recent randomized, double-blind, clinical trial (Rezaei, Akhlaghi, Sasani, & Barati Boldaji, 2019), the effect of olive oil intake was studied on 66 subjects with NAFLD during 12 weeks. A small amount of olive oil (20 g/days) was enough to reduce weight, waist circumference, blood pressure, and fatty liver grade in these patients.

Several studies have also been conducted on healthy subjects. Yaqoob et al. (Yaqoob et al., 1998) conducted a double-blind,

randomized, controlled trial on healthy men to investigate the correlation between olive oil consumption (8 weeks) and immune function. Olive oil, through rich amount of monounsaturated fatty acids, decreased the expression of intercellular adhesion molecule 1 (ICAM-1) by peripheral blood mononuclear cells.

Visioli et al. (Visioli et al., 2000) studied the correlation between the antioxidant activity of olive oil and oxidative stress. Olive oil intake (50 g) decreased urinary excretion of 8-iso-PGF $_{2\alpha}$  - a biomarker of oxidative stress. PC in olive oil also influenced the oxidative/antioxidative status (Weinbrenner et al., 2004). The intake of 25 ml for 4 days decreased plasma oxidized LDL, 8-Oxo-2'-deoxyguanosine and MDA in healthy subjects with a remarkable increase in HDL-C and GPX. Similar findings were obtained by Salvini et al. (Salvini et al., 2007). EVOO performed its positive effects through PC involved in reduction of DNA damage in healthy women.

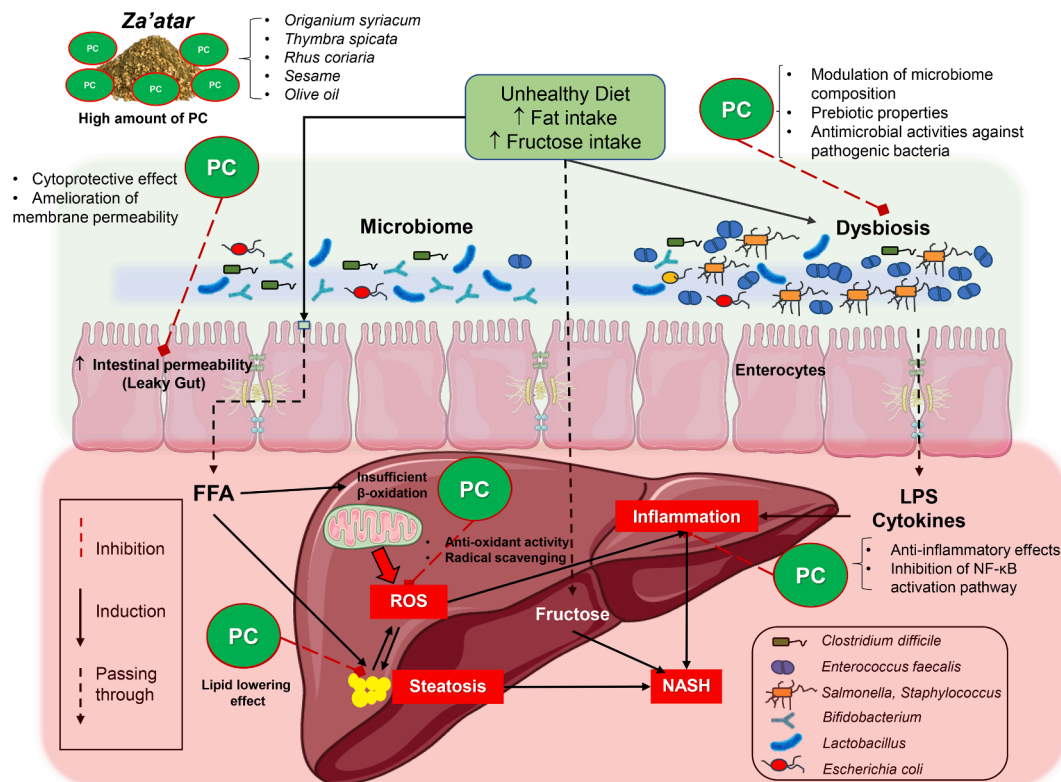
#### 5. Overall conclusions about Za'atar as functional food

Foods rich in polyphenols are found abundantly in plants, and have become an emerging field of interest in nutrition in recent decades (Esteban-Fernández, Zorraquín-Peña, González de Llano, Bartolomé, & Moreno-Arribas, 2017). As discussed above, Za'atar mixture contains a high number of different polyphenols that, as single agents, are known to promote beneficial effects on both cellular and animal models, and on humans. Besides, many studies suggest that although many single plant-based bioactive compounds could exert different health-promoting effects, the combination of different plant-based foods may exhibit additive and/or synergistic interactions among their different phytochemicals, which may enhance their bioactivity (Zehua Liu, Luo, Jia, Wang, & Li, 2016). In this context, we suppose that, respect to the single ingredients, Za'atar mixture could exhibit a greater beneficial effect than the single agents, therefore, Za'atar mixture could have a direct impact on human health and could promote pharmacological effects, in particular for metabolic disorders such as NAFLD, cardiovascular, and peripheral vascular diseases. More studies are required in this respect.

The beneficial effects of Za'atar might involve the interaction between polyphenols and gut microbiome in health and during dysbiosis (Fig. 3). Gut microbiota contribute to the biotransformation of polyphenols into metabolites, and this will result in an increased bioavailability and bioactivity of polyphenols. Polyphenols, in turn, can modulate the composition of gut microbiota, mostly through the inhibition of pathogenic- and the stimulation of beneficial bacteria. This modulation may improve essential functions exerted by microbiota with beneficial outcomes on host health, as shown in Fig. 3.

The beneficial effects of Za'atar intake on the hepatic lipid metabolism and, consequently, on NAFLD prevention and/or improvement can be influenced primarily by its high phenolic content. As reported in Table 4 and Table 5, Za'atar components and their main compounds may prevent the development of NAFLD and related diseases by improving both plasma lipid and cholesterol levels and reducing body fat accumulation. As shown in Fig. 4, CVL, RA, and GA can regulate three major transcriptional factors controlling multiple pathways involved in hepatic carbohydrate and lipid metabolism: i) activation phosphorylated AMP-activated protein kinase; ii) activation of hepatic peroxisome proliferator-activated alpha enhancing fatty acid oxidation; iii) suppression of sterol regulatory element binding protein-1 (SREBP-1) and results in the inhibition of glycolysis and of de-novo lipogenesis. Ultimately, CVL, RA, and GA promote a shift in metabolism toward fatty acid oxidation and away from fatty acid synthesis and storage and may positively affect NAFLD.

The health-promoting effects of polyphenols are strictly related to the consumed amount but also on their bioavailability, as they are absorbed at the intestinal level (Wan, Co, & El-Nezami, 2020). Dose-dependent effects of polyphenols play a crucial role in their physiological actions, also at low concentration, with probiotic,



**Fig. 3.** Putative mechanisms in the gut-liver axis of PC present in high amount in Za'atar mixture that contribute positively to NAFLD. PC modulate the imbalance of gut microbiome (dysbiosis) that occur after unhealthy diet intake. In particular, PC may modulate the composition of the gut microbiota, likely through the inhibition of pathogenic bacteria and the stimulation of beneficial bacteria species. (Ozdal et al., 2016). PC also protect the intestinal barrier against dysfunction. Imbalance of microbiota deliver in liver metabolites and inflammatory mediators that trigger liver oxidative stress and inflammation (Abenavoli et al., 2021; Etxeberria et al., 2013). In addition, high fatty acid intake may develop lipid accumulation in liver causing steatosis. Excess lipid accumulation in the liver cells is not only a mediator of metabolic syndrome but also could progress to nonalcoholic steatohepatitis, the necrotic and inflammatory form of hepatic steatosis. PC ameliorate the lipid accumulation by regulation the lipid metabolism. Finally, PC exert a potential antioxidant activity by direct scavenging of free radical or modulating the mitochondria-mediated oxidative defense; moreover, PC reduce the NF- $\kappa$ B activation pathways and protect against liver inflammation (Cory, Passarelli, Szeto, Tamez, & Mattei, 2018). **Abbreviations:** FFA, free fatty acids; LPS, lipopolysaccharide; NASH, nonalcoholic steatohepatitis; NF- $\kappa$ B, nuclear factor  $\kappa$ B; PC, phenolic compounds; ROS, reactive oxygen species.

antioxidant, and anti-inflammatory functions, as well as through modulation of lipid metabolism (Basu, Masek, & Ebersole, 2018; Moorthy, Chaiyakunapruk, Jacob, & Palanisamy, 2020). However, this effectiveness depends mainly on the amount or dose that must be taken, which in turn will activate specific biological functions without the other, and this is known as “dose-related activity”. A panel of studies showed that polyphenols exert dose-related activities. For example, CVL showed a dose-related inhibition of pathogen growth starting with 0.15 mg/g (Ultee, Slump, Steging, & Smid, 2000). While, 10 mg/kg of resveratrol is enough to enhance the locomotor activity in rats (Girbovan, Morin, & Plamondon, 2012). Moreover, quercetin (10–60 mg/kg) can inhibit both phases of formalin-induced pain, with median infective dose values of 374.1 (68.0–402.0) mmol/kg and 103.0 (45.0–201.0) mmol/kg, for the neurogenic and inflammatory phases, respectively (Filho, Filho, Olinger, & de Souza, 2008). Silybin, as well, is able to inhibit dose-dependently (25–50  $\mu$ M) growth factor-induced pro-fibrogenic actions of activated human hematopoietic stem cell, including cell proliferation, cell mortality, and *de novo* synthesis of extracellular matrix component (Trappoliere et al., 2009).

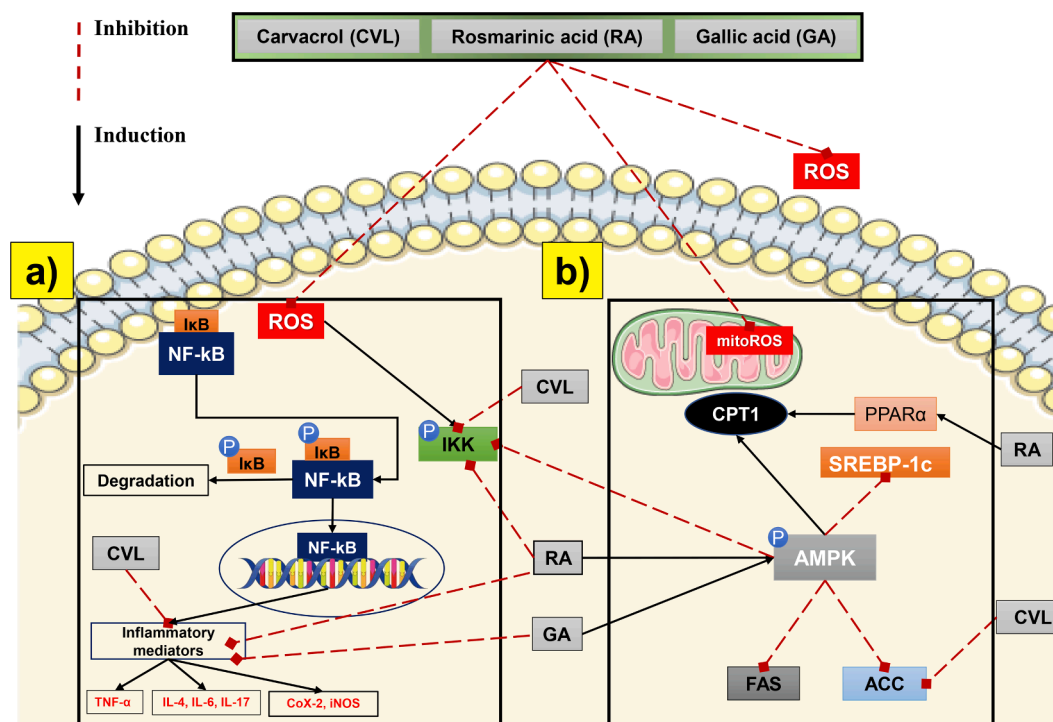
Typically, Lebanese people consume daily around 10 to 20 g of Za'atar mixture accompanied by 10 to 20 g of olive oil and between 100 and 150 g of bread (CIHEAM-MAI.B, 2008). As said before, Za'atar mixture contains about 6 to 12 g of leaves of Za'atar plants (*O. syriacum* and *T. spicata*), 1.2 to 2.4 g of sumac (*R. coriaria* blend fruits), and 2.8 to 5.6 g of sesame seeds. According to the clinical trials (Table 5), the consumption of 1 or 2 g of sumac per day could reduce lipid and cholesterol levels as well as blood pressure. In addition to that, it could

decrease hepatic fibrosis, modulate liver enzymes (ALT and AST), and ameliorate insulin resistance. Accordingly, comparing these dose-related activities with the amount of sumac obtained from Za'atar mixture (1.2 to 2.4 g), we will find that it is more than sufficient to activate the aforementioned biological properties.

To best of our knowledge, different studies (Dorman et al., 2004; Mohamad Khalil, Hala Khalifeh, et al., 2020; Shen et al., 2010) cited that 1 g of *T. spicata* and *O. syriacum* leaves may contain 20 to 200 mg of RA and 30 to 180 mg of CVL. Thus, the intake of 6 to 12 g of *O. syriacum* and *T. spicata* in the Za'atar mixture could provide 120 to 2400 mg of RA and 180 to 2160 mg of CVL. According to Table 5, consumption of 50 to 200 mg of RA as well as 1.2 mg/kg body weight of CVL per day could reduce asthma and allergic symptoms as well as inflammation and pain. Interestingly, Za'atar mixture could provide the necessary amount of RA and CVL to activate the health effects on humans. Moreover, a small amount of RA and CVL can influence the intestinal microbial composition, and therefore the metabolites available for interaction with relevant targets.

## 6. Conclusions

The economic and social commission for western Asia (ESCWA) in 2010 defined the Lebanese Zaatar, whether fresh or dried, as a common item in Mediterranean diets and is witnessing burgeoning in consumer demand (ESCWA, 2010). In addition, the joint FAO/WHO food standards programme codex alimentarius commission reported the Za'atar mix standardization, types, compositions and preparations, and



**Fig. 4.** Potential mechanisms underlying the effect of the main PC present in *Thymbra spicata*, *Origanum syriacum* and *Rhus coriaria* in NAFLD. Based on the *in vitro* and *in vivo* studies reported in Tables 4 and 5, carvacrol (CVL), Rosmarinic acid (RA) and Gallic acid (GA) may protect hepatocytes by: a) Rescue cell injury and inflammation by attenuation the NFκB activation pathway; b) Improve lipid metabolism by modulation of AMPK activation that resulting in SREBP-1c down-regulation (reducing de novo lipogenesis) and PPARα up-regulation (increasing β-fatty acid oxidation). **Abbreviations:** ACC, acetyl-CoA carboxylase; COX-2, cyclooxygenase 2; CPT-1, carnitine palmitoyl transferase 1; CVL, Carvacrol; FAS, fatty acid synthase; GA, gallic acid; IκB, IκB kinase; IL-4, interleukin 4; IL-6, interleukin 6; IL-17, interleukin 17; iNOS: inducible nitric oxide synthase; mitoROS, mitochondrial reactive oxygen species; NF-κB, nuclear factor κB; p-AMPK, phosphorylated AMP-activated protein kinase α; ROS: Reactive oxygen species; TNFα: Tumour Necrosis Factor alpha.

included the mixed Za'atar as "Herbs-spices" category (FAO/WHO, 2020), thus, Za'atar can be considered as a full description of MD, with optimal nutraceutical proprieties, mainly due to the biological properties of its main constituents (i.e. *O. syriacum*, *R. coriaria*, sesame seeds, and olive oil).

Available evidence, especially those reported by Randomized Clinical Trials (RCT), suggest that the regular daily intake of Za'atar, represents a mixture of health food ingredients that is able to provide beneficial effects on human health through a combined and modulated action on metabolic pathways, oxidative balance, chronic inflammation, and gut microbiota. Additional studies are needed on the role of Za'atar mixture as a useful preventive and curative tool

## 7. Perspective

Despite the enormous beneficial effects reported here of Za'atar component and/or single major compounds, unfortunately, the bioactivity of the whole mixture is not yet studied and detailed. Thus, further animal and human studies are highly needed to further elucidate translational aspects and to fully characterize Za'atar (whole mixture) as a preventive and curative tool in the short- medium term., and to proof its effectiveness as a natural- and plant-based healthy food. In fact, the precise amount of Za'atar mixture useful to obtain beneficial health effects is not identified yet, and that could be the reason standing behind the lack of clinical trials. Accordingly, our future molecular and clinical studies followed by suitable statistical tests for data analysis, will focus on the combined effects of Za'atar mixture by exploring its synergistic effects, testing its clinical efficacy on a specific target of subjects, and evaluating the Za'atar-health relationship validity.

### Consent for publication

Not applicable

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### URL (WebPage)

- Nutritionix Grocery Database, USA: <https://www.nutritionix.com/i/arz/zaatar-lebanese-blend/5be7d4d5406d6dc931fc5241>.



- 2019 Lebanon's 6th national report to the convention on biological diversity: <https://www.cbd.int/doc/nr/nr-06/lb-nr-06-en.pdf>

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