Journal of Functional Foods 87 (2021) 104811

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Role of Sumac (*Rhus coriaria* L.) in the management of metabolic syndrome and related disorders: Focus on NAFLD-atherosclerosis interplay

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ARTICLE INFO

Keywords:
Rhus coriaria L. (sumac)
Functional foods
Metabolic diseases
Medicinal plants
Atherosclerosis

ABSTRACT

Sumac (*Rhus coriaria* L.) is a commonly used spice in the Mediterranean region and considered as healthy food ingredients. The beneficial value of sumac is well documented in folk medicine. Accumulating data explored the phytochemical, nutritional and therapeutic proprieties suggesting sumac as a potential functional food. Here, we discuss the general and scientific aspects of sumac. Sumac is rich in different polyphenolic compounds such as flavonoids, tannins, and phenolic acids. The potential therapeutic effects of sumac have been studied in various cellular and animal models, as well as in human. These reports suggest that Sumac has potential effect against oxidative stress, inflammation, obesity, hyperglycemia, hypercholesterolemia, and hyperlipidemia, which represent key pathogenic mechanisms contributing to cardio-metabolic, liver, and cancer diseases. Clinical studies using sumac or its major compounds, suggest that this herbal product may represent a useful therapeutic tool in the management of metabolic-related conditions such as liver-atherosclerosis complications.

1. Introduction

Metabolic syndrome is the medical term which defines a cluster of conditions or metabolic disorders, including hypertension, hyperglycaemia/insulin resistance, obesity and dyslipidaemia, coexisting in an individual. All these disorders may lead to an increased risk of type 2 diabetes, non-alcoholic fatty liver diseases (NAFLD), cardiovascular disease (CVD) and stroke (Simmons et al., 2010).

Functional foods (FFs) are those foods that may promote health benefits beyond their supply of essential nutrients (e.g., vitamins and minerals) (Griffiths, Abernethy, Schuber, & Williams, 2009). Based on its basic nutritional and nutraceutical properties, a functional food can decrease the risk for the onset of many chronic diseases, and might contribute to health benefits. Active components of FFs, for example, can play beneficial effects on metabolic disorders, such as hyperlipidemia, type 2 diabetes, obesity/overweight, NAFLD, hypercholesterolemia and inflammation (van den Driessche, Plat, & Mensink, 2018).

In the Mediterranean region, especially in the Middle East, *Rhus coriaria* L., commonly known as "Sumac", is a popular spice widely employed as condiment and souring agent (Tohma, Altay, Köksal, Gören, & Gülçin, 2019). Powdered sumac fruit, for example, is added to salad and meat to add lemony taste. In some Eastern Mediterranean countries powdered sumac is used in the composition of Za'atar, a mixture of a homemade earthy and herby savoury blend of dried thyme-like plants such as *Origanium syriacum* and *Thymbra spicata*, used for a variety of dishes especially for the Lebanese flatbread "Mankouche" (Alwafa, Mudalal, & Mauriello, 2021). In addition to its culinary usage, Sumac has a long history in traditional medicine, to cure liver diseases, diarrhea, urinary problems, and gastric ulcers (Sakhr & El Khatib, 2020).

The potential therapeutic effects of *R. coriaria* has described in both cellular and animal models, as well as in clinical trials. Findings suggest that Sumac has potential antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic and neuroprotective activities (Akbari-Fakhrabadi, Heshmati, Sepidarkish, & Shidfar, 2018; Alsamri, Athamneh, Pintus,

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https://doi.org/10.1016/j.jff.2021.104811
Received 7 August 2021; Received in revised form 18 October 2021; Accepted 18 October 2021
Available online 23 October 2021

Table 1
Clinical trials studies involved NAFLD patients associated with atherosclerosis and related diseases.

Issue	Patients	Duration	Treatment	Findings	Reference
Endothelial dysfunction-NAFLD	34 (NAFLD patients) 20 (control)	16 weeks	moderate-intensity exercise training	Endothelial dysfunction in NAFLD could be reversed by exercise training	(Pugh et al., 2014)
Carotid intima-media thickness (marker of atherosclerosis) - NAFLD	29 (with T2DM and NAFLD) 29 (with T2DM without NAFLD)	8 months	Metformin + liraglutide 0.6 mg/day for 2 weeks, followed by 1.2 mg/day	Treatment in patients with T2DM and NAFLD reduced carotid IMT	(Rizvi et al., 2015)
High-risk coronary plaque at coronary CT angiography - NAFLD	445 patients from the coronary CT angiography arm (182 with NAFLD)	–	–	There is an association between NAFLD and advanced high-risk coronary plaque	(Puchner et al., 2015)
Augmentation index -adiponectin	63 patients with NAFLD)	12 months	Daily metformin and placebo	Metformin caused a decrease in augmentation index in NAFLD patients	(Shargorodsky, Omelchenko, Matas, Boaz, & Gavish, 2012)
NAFLD – carotid intima-media thickness (CIMT)	92 patients with NAFLD	15–18 months	n-3 PUFA (Omacor / Lovaza 4 g/die) or placebo	Improvement of NAFLD severity is independently associated with reduced CIMT progression	(Bhatia et al., 2016)
NAFLD	63 patients with NAFLD	4 months	Daily metformin or placebo	Metformin caused beneficial vascular effect and improvement in glucose and lipid metabolism	(Sofer, Boaz, Matas, Mashavi, & Shargorodsky, 2011)
LDL-migration index – NAFLD / NASH	156 with NAFLD (53 with NAFL and 103 eith NASH) 69 with NAFLD (25 with NAFL and 44 with NASH)	–	–	LDL-MI was higher in patients with NASH that with NAFL, so the risk of atherosclerosis disease may be higher in NASH that NAFL	(Imajo et al., 2014)
Dietary fructose reduction and NAFLD – cardiovascular disease	24 overweight adolescents with hepatic fat	4 weeks	Dietary with fructose only or glucose only beverages	Reduction of fructose improves several important factors related to cardiovascular disease, without an improvement in hepatic steatosis	(Wojcik-Cichy et al., 2018)
NAFLD – early carotis atherosclerosis	54 non-alcoholic steatohepatitis 54 IGT 54 healthy subjects	–	–	In IGT subjects the increase of CIMT in presence of NASH cannot be mediated by insulin resistance, so NAFLD and NASH may dependent on other factors	(Pagano, Vecchio, Giangreco, & Neri, 2012)

Abbreviation: NAFLD, non-alcoholic fatty liver diseases; T2DM, type 2 diabetes mellitus; IMT, intima media thickness; CIMT, carotid intima-media thickness; LDL, low-density lipoprotein; NASH, nonalcoholic steatohepatitis; NAFL, non-alcoholic fatty liver; IGT, impaired glucose tolerance.

Eid, & Iratni, 2021; Khalil et al., 2021). To date, many phytochemicals have been characterized and isolated from *R. coriaria* and these include organic acids, phenolic acids, phenolic compounds conjugated with malic acid derivatives, flavonoids, isoflavonoids, hydrolysable tannins, anthocyanins, terpenoids, and other compounds such as butein, iridoid, and coumarin derivatives (Abu-Reidah, Ali-Shtayeh, Jamous, Arráez-Román, & Segura-Carretero, 2015).

In this review, we discuss the main characteristics of sumac as adjuvant in metabolic disorders, namely the NAFLD-atherosclerosis axis, looking at the translational value of basic experiments.

2. The metabolic context

Metabolic disorders represent a major health problem worldwide, and the metabolic syndrome (MetS) is the multifactorial manifestation which includes particularly abdominal obesity, insulin resistance often leading to type 2 diabetes mellitus, release of adipocyte cytokines (adipokines), vascular endothelial dysfunction, dyslipidemia, arterial hypertension, vascular inflammation, cholesterol gallstones and liver steatosis. All together, these conditions promote the development of atherosclerotic cardiovascular disease in both individuals with excess of total body weight (Defronzo & Ferrannini, 1991; Koh, Han, & Quon, 2005; Lindsay & Howard, 2004) or with abdominal obesity who do not have an excess of total body weight (Conus et al., 2004; Richelsen & Pedersen, 1995; Ruderman, Chisholm, Pi-Sunyer, & Schneider, 1998; St-Onge, Janssen, & Heymsfield, 2004).

Although cancer has historically been viewed as a disorder of proliferation, recent evidence has suggested that it should also be considered a metabolic disease (Coller, 2014). For instance, obesity and overweight are linked to several cancers (Must et al., 1999). Presently, the metabolic changes in tumor surrounding microenvironment as chronic inflammation state, presence of dyslipidemia and insulin-resistance are substantially accepted features which contribute to increased cancer risk (Cazzaniga & Bonanni, 2018). In 2008, a study revealed that an increase in the BMI is associated with an enhanced risk of several malignancies and overall with 14% of all cancer deaths in men and with 20% of all cancer deaths in women (Renehan, Tyson, Egger, Heller, & Zwahlen, 2008). This work was updated by a recent study done by Bhaskaran et al. in 2014. They studied the association of BMI with the risk of 22 specific cancers. Their findings showed that indeed a high BMI is associated with cancer risk, with substantial population-level effects (Bhaskaran et al., 2014). In the other hand, angiogenesis which plays a significant role in tumor progression is also a major player in the context of further metabolic diseases, especially in obesity (Breier, Chavakis, & Hirsch, 2017). Therefore, cancer prevention in patients with MetS is to prevent risk factors (Uzunlulu, Telci Caklili, & Oguz, 2016). Lifestyle changes including weight loss, sufficient physical activity, and an appropriate diet, are known to decrease cancer risk in normal population (Giacosa et al., 2013).

2.1. Atherosclerosis

Atherosclerosis is a process that causes disease of the coronary, cerebral, and peripheral arteries and the aorta (Faxon et al., 2004; Libby, Ridker, & Hansson, 2011). The pathogenesis of atherosclerosis involves multiple factors such as endothelial dysfunction (Kitta et al., 2009) chronic inflammatory changes (e.g., release of inflammatory factors, cytokines, leukocyte activation, dyslipidemia, hypertension, smoking, diabetes, tissue factors (i.e., release of angiotensin II, endothelin-1) (Weber & Noels, 2011). Atherosclerosis is the leading cause of cardiovascular disease (CVD) with high rates of mortality and morbidity worldwide, due to coronary, carotid artery disease, renal artery stenosis, and peripheral artery disease. Myocardial infarction and stroke are two typical consequences of atherosclerosis (Wang, Garruti, Liu, Portincasa, & Wang, 2017). At cellular level, different cell types are involved in atherosclerosis initiation and progression, including immune cells (monocytes), smooth muscle, and endothelial cells. Thus, the endothelial dysfunction and damage associated with increasing inflammatory

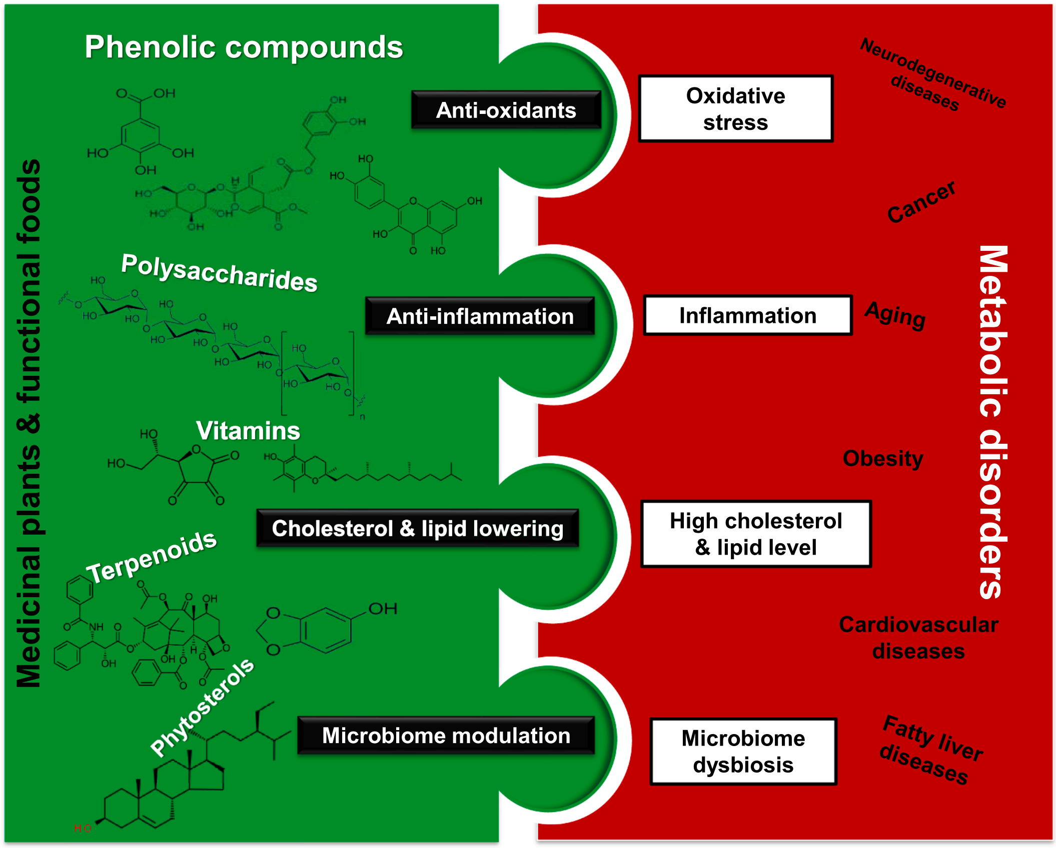

Fig. 1. A schematic image showing the efficacious role of medicinal plants & functional foods compounds (green piece) on metabolic disorders and their related diseases (red piece). MetS risk factors include inflammation, oxidative stress, high cholesterol & lipids level, and microbiota dysbiosis. Medicinal plants, functional foods include phenolic compounds, polysaccharides, vitamins, terpenoids, and phytosterols. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mediators could increase the membrane permeability, enhance monocyte adhesion and infiltration, and augment release of growth factors which play a crucial role in the initiation of atherosclerosis.

2.2. Nonalcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in developed countries and is associated with obesity, dyslipidemia, diabetes, and metabolic syndrome. NAFLD is due to an excessive accumulation of toxic lipids in the hepatocytes independently from alcohol intake, which may encompass a wide spectrum of liver pathologies, including simple steatosis to nonalcoholic steatohepatitis, cirrhosis, and even hepatocellular carcinoma. The hepatic damage is mediated by various factors, such as mitochondrial damage, endoplasmic reticulum stress, production of ROS (Reactive Oxygen Species) and stimulation of TNFα (Tumor Necrosis Factor) production, which contribute to the progression of NAFLD (Bessone, Razori, & Roma, 2019; Tilg & Moschen, 2010). In addition, insulin resistance plays a central role in the development of NAFLD, which causes an increase in the hepatic absorption of free fatty acids, as well as a greater esterification to triglycerides. Insulin resistance also causes hyperglycemia which is also connected to NAFLD.

3. Atherosclerosis-NAFLD interplay

NAFLD often associated with the MetS may have a direct impact on the endothelial dysfunction and consecutively represents a risk factor for atherosclerosis and cardiovascular diseases (Stols-Gonçalves, Hovingh, Nieuwdorp, & Holleboom, 2019). Clinically, they are highly prevalent of atherosclerosis in NAFLD patients, due to the presence of shared risk factors (Wojcik-Cichy, Koslinska-Berkan, & Piekarska, 2018). Some researchers have pointed out that NAFLD is likely associated with increasing CVD risk and have raised the possibility that NAFLD might be not only a marker but also an early mediator of atherosclerosis (Han et al., 2019). Therefore NAFLD can be defined as atherogenic (Kvietys & Granger, 2012). So, the question is: if NAFLD is a causal mediator and can trigger a systemic inflammation independently of traditional cardiovascular risk factors (age, sex, body mass index, arterial hypertension, diabetes mellitus, dyslipidemia, current or former smoking), which factors are involved?

Several factors which participate at this interplay such as hyperlipidemia and hypertriglyceridemia and endothelial dysfunction are observed in NAFLD patients. In fact, excess LDL oxidizes on the artery wall, attracting macrophages, which originate plaques and transform into foam cells (Stols-Gonçalves et al., 2019). In addition, the liver in NAFLD patients produce pro-coagulant and pro-inflammatory factors such as TNFα and IL-6, IL-8 as well as fibrinogen and plasmin activator-1, these mediators seem to be associated with obesity and metabolic abnormalities in general (Glass et al., 2018; Stols-Gonçalves et al., 2019). In the following table (Table 1), we list several clinical trials that link NAFLD and CVD.

The treatment of MetS, and associated atherosclerosis and NAFLD is complex, and implies multilevel approaches. For NAFLD, however, no specific drug-based approved pharmacological treatment is available so far.

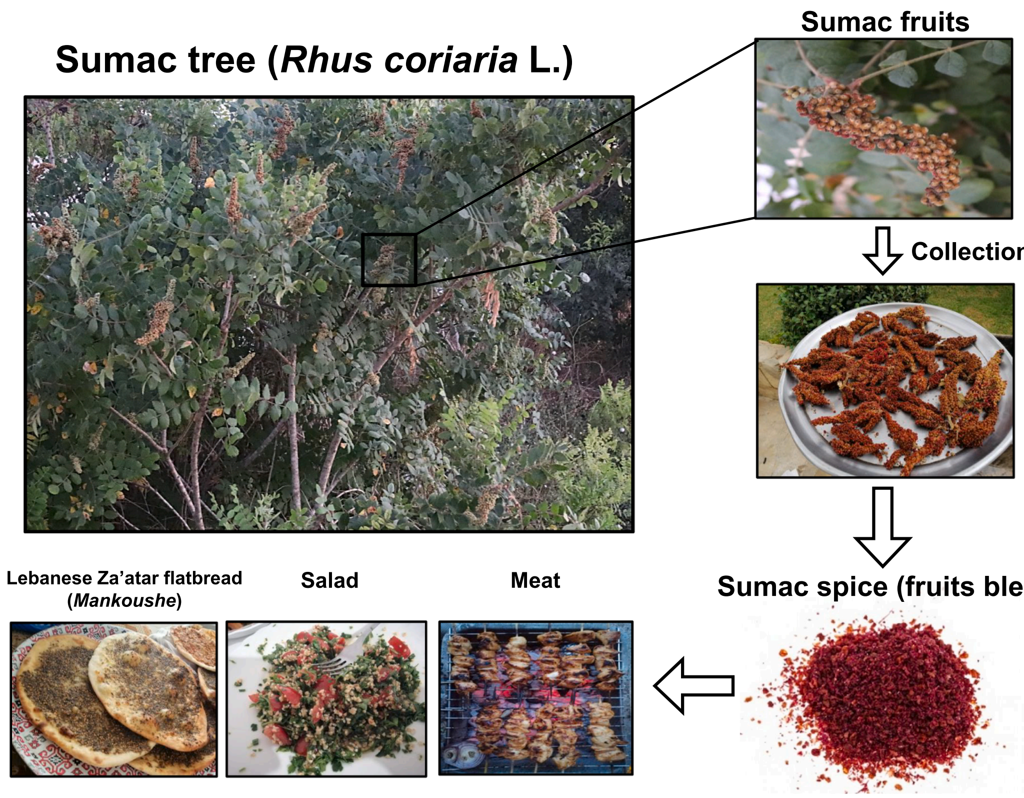

Fig. 2. *Rhus coriaria* L. (Sumac) tree, fruits and spice; sumac fruits powder is widely used as flavor and soaring agent in the Mediterranean cuisine: salad, meat, Za'atar and spice mixture.

4. Functional foods

It has been known for a long time the relationship between the food we eat and our health (Serafini & Peluso, 2016). The current concept of functional foods has resulted from the gradual recognition that healthy diets result from eating nutritious foods and from the identification of the mechanisms by which foods modulate metabolism and health.

The term 'functional food' was coined in Japan in the early 1980s. Although there is no universal definition of functional food, the simplest definition is "processed foods having disease-preventing and/or health-promoting benefits in addition to their nutritive value." FFs overlap with nutraceuticals, medical foods ext. Functional food has a positive impact on an individual's health, physical performance, or state of mind, in addition to its nutritious value.

Nevertheless, lifestyle (i.e., diet and physical exercise) aiming to maintenance of ideal body weight or weight loss in overweight and obese individual to try to reach ideal body weight, remain valid choices (Amato et al., 2017). In addition, the possibility exists that drugs may bring negative side effects. In this respect, current research is focusing on natural products, their active compounds, and functional foods. As shown in Fig. 1, plant-derived natural products such as polyphenols, polysaccharides and phytosterols, which are known for their safety and efficacy, can provide satisfactory effects on MetS and risk factors such as inflammation, oxidative stress, high cholesterol and lipids level, and microbiota dysbiosis. In this regard, several recent reviews have discussed the evidence from experimental and clinical studies regarding the potential beneficial effects of plant-derived natural products for the treatment or prevention of MetS including NAFLD and atherosclerosis (Abenavoli et al., 2021; Leuci et al., 2020; Li et al., 2020; Rochlani, Pothineni, Kovelamudi, & Mehta, 2017; Simental-Mendía et al., 2021).

In the following section we highlight the potential translational value of sumac as therapeutic agent especially in NAFLD and atherosclerosis.

4.1. History and general aspect of sumac

Sumac (pronunciation: Soummaq), is the common name used in the Mediterranean region to indicate the spice product of the fruits of *R. coriaria,* a flowering shrub belonging to the Anacardiaceae family. *R. coriaria* shrub grows in high plateau areas of the Mediterranean like Sicily, due to its wild, rocky lands. Sumac also grows in Lebanon, Turkey and can be found in parts of Iran.

As shown in Fig. 2 the processed sumac takes on a dark red-burgundy color and the texture of ground nuts. It has a similar smell and taste to lemon but is not as sour. Sumac is widely used as an acidulant in Arabic and Lebanese cooking, and similar to salt, it brings out the natural flavors of the foods it is cooked with. Since ancient time, in Mediterranean cuisine, sumac has been used as souring agent for drink, appetizer and sauce (Abu-Reida, Jamous, & Ali-Shtayeh, 2014). The Greek physician Pedanius Dioscorides (c. 40–90 AD) reported in his medical book De Materia Medica ("On Medical Matters") about the healthful properties of sumac as a diuretic and anti-flatulent. *R. coriaria* has been used commonly in folk medicine as remedy of ulcer, hepatic disease, diarrhea, and animal bites (Norton, 2005).

The Ancient Arabic book "*A-lma'tmd fi al-a'douiah al-mfrdah*" (English translation: The approved book in single drugs) is an interesting collection of many valuable herbal medicines which describes the beneficial effects of many medicinal plants that have been used traditionally. The book reported that Sumac is the fruit of a tree that grows in the rocks of about two meters in length; it has a long leaf, and a fruit that has the shape of clusters with reddish color like blood, that is why it is used as dye or colorant. It is also used in food for its sourness, and it can be mixed and cooked with meat. Sumac's benefits are found in the cortex of its fruits; it benefits chronic diarrhea, vomiting, eyes twitching,

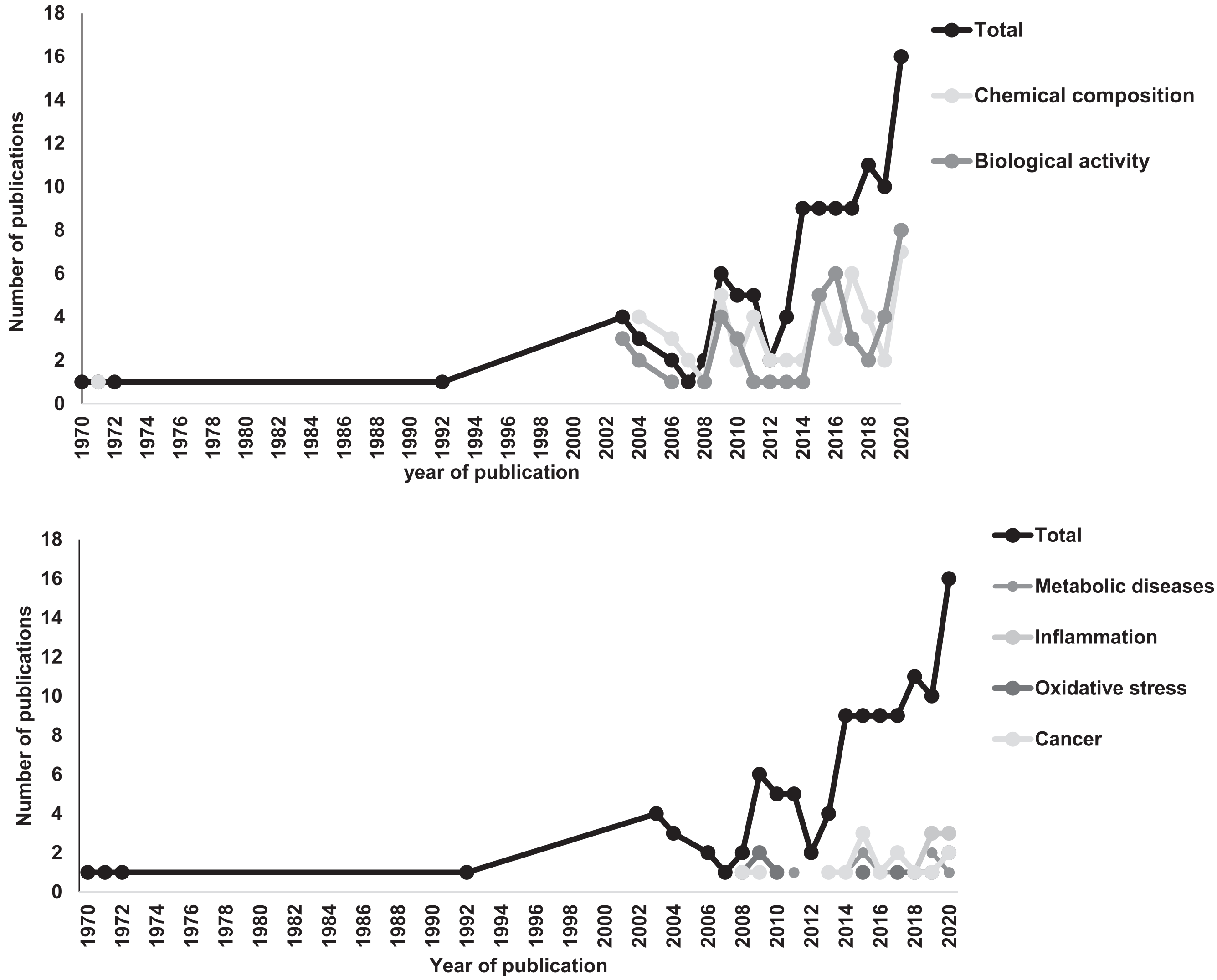

Fig. 3. Graphs representing the growing publication numbers of scientific articles from 1970 to 2020. These publications studied sumac chemical composition and its biological activities. (https://pubmed.ncbi.nlm.nih.gov/?term=rhus+coriaria).

stops bleeding, treats scars, ears infection and Hemorrhoids. The book also report that the water infusion of sumac can reduce inflammation, relax and protect the stomach, protect the liver and helps the yellow material (Bile) to reach the intestine (al-Turkomani, 1222 – 1297 CE).

Nowadays in many Mediterranean countries, traditional societies still belief in sumac healing powers. Sumac is a powerhouse of antioxidants, which are known to prevent cancer, heart disease, and signs of aging. Others also report its use in improving wound healing and as an antimicrobial agent (Alsamri et al., 2021).

Interest for *R. coriaria* has been growing among scientists and pharmacologists, as shown in Fig. 3, over the last decades (from 1970 to 2020). Many studies were conducted to determine the chemical composition and to evaluate biological and pharmacological effects of *R. coriaria* (Fig. 3). These studies were of great importance in terms of scientific exploration of the biologically active agents that are traditionally employed in folk medicine and food (Süntar, 2020).

Moreover, the toxicological profile of *R. coriaria* was evaluated in different studies and showed that sumac consumption even at high concentration (up to 5 g/kg) is totally safe in animal models (Doğan & Çelik, 2016) (Ahangarpour et al., 2017) (Janbaz, Shabbir, Mehmood, & Gilani, 2014).

In the following sections we report the recent advances in phytochemical compositions and pharmacological effects of *R. coriaria* with special focus on the metabolic disorders.

4.2. Chemical composition of *R. coriaria*

Considering that *R. coriaria* has several uses in Mediterranean food and folk medicine and has demonstrated many beneficial health effects against many human illnesses, the phytochemical finger-print screening of sumac has illuminated a broad catalog of health-promoting polyphenolic components and have been extensively investigated and reported by many studies. To date, over 200 compounds have been identified in *R. coriaria* extracts. The Fig. 4 reports the different class of the most important phytochemical constituents of sumac such as hydrolysable tannins, phenolic acids, anthocyanins, flavonoids, organic acids, terpenoids, and essential oils (Fig. 4).

Hydrolysable tannins derivatives are the most abundant compounds in sumac, especially gallic acid, methyl gallate and derivatives such as galloylhexose, O-galloylnorbergenin isomers, digalloyl-hexoside, methyl digallate isomers, trigalloyllevoglucosan, digallic acid, hexagalloyl-hexoside, isomers of hinokiflavone or amenthoflavone or agathisflavone (Gök, Deliorman Orhan, Gürbüz, & Aslan, 2020; Regazzoni et al., 2013). Organic acids are also present of *R. coriaria* fruits such as malic acid isomers and derivatives which are reported to be the most abundant organic acid in *R. coriaria.* In addition, phenolic acids and

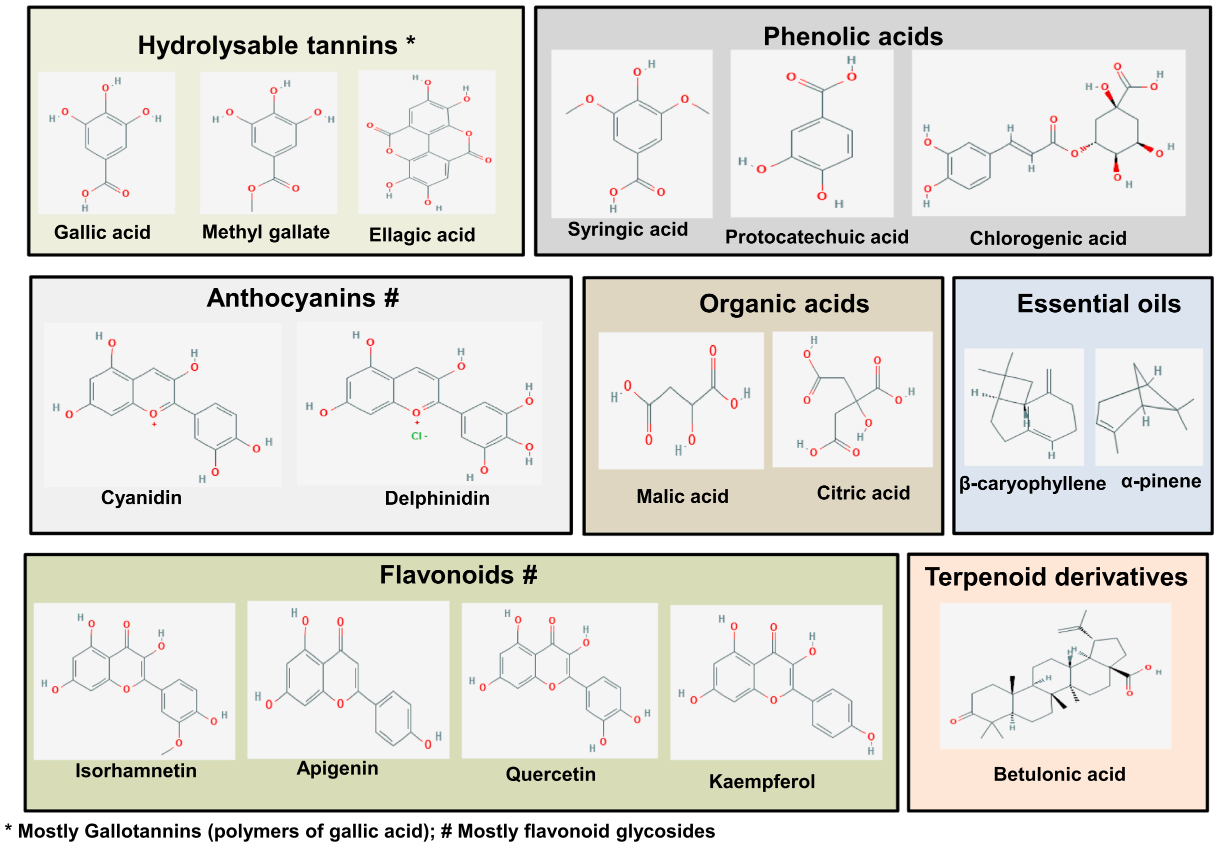

Fig. 4. Structure of the most important compounds from *Rhus coriaria fruit* "Sumac" (PubChem).

Table 2
Nutritional values of Sumac, values refer to 100 g of sumac.

Content in 2.7 g (1 tap spoon)	% Daily Value *	Content in 100 g
Total Fat 0.4 g	1%	14.4 g
- Saturated Fat 0.1 g	0%	2.6 g
- *Trans* Fat 0 g	0%	0 g
- Polyunsaturated Fat 0.2 g	0%	8.1 g
- Monounsaturated Fat 0.1 g	0%	3.3 g
- Cholesterol 0 mg	0%	0 mg
Sodium 77 mg	3%	2849 mg
Potassium 53 mg	2%	1961 mg
Total Carbohydrates 1.3 g	0%	48.1 g
Dietary Fiber 0.9 g	4%	34.8 g
Sugars 0.2 g	0%	7 g
Protein 0.4 g		13.3 g
Vitamin A	16%	
Vitamin C	0%	
Calcium	0.7%	
Iron	2.6%	

* Percent Daily Values are based on a 2000 calorie diet.
Based on Nutritionix Grocery Database (https://www.nutritionix.com/food/sumac)

derivatives are found abundantly in sumac, such as protocatechuic acid hexoside, syringic acid hexoside and coumaryl-hexoside, caffeoylquinic acid and quinic acid as well as phenolics conjugated with glycoside-malic acid including galloyl-hexose-malic acid isomers, of kaempferol hexose-malic acid isomers, myricetin-hexose malic acid isomers, and quercetin-hexose malic acid (Abu-Reidah et al., 2015).

Flavonoid and flavonoid derivatives are present in large quantity in *R. coriaria* fruits such as isorhamnetin, myricitrin, apigenin, quercetin, chrysoeriol, eriodictyol and kaempferol as aglycone or as glycoside derivatives (Abu-Reidah et al., 2015; Mehrdad et al., 2009). Cyanidin and delphinidin derivatives are the most anthocyanin presents in sumac that gives the rich red color to sumac fruits pericarp (Regazzoni et al., 2013).

At last not least, another class of secondary metabolites is also present in Sumac; Monoterpene and sesquiterpene hydrocarbons were the most abundant classes of terpenes that form the major constituent of sumac essential oils. An Italian study found that β-caryophyllene and α-pinene were the main constituents in the majority of the examined samples, in another study, major identified components included, additionally to α-pinene, naphthalene and o-cymene in different region area around the Mediterranean (Farag, Fayek, & Abou Reidah, 2018; Reidel, Cioni, Majo, & Pistelli, 2017).

Additionally to the listed phytochemical constituents, Sumac composition is also rich in fatty acids, minerals such as sodium, potassium, calcium and iron, and in dietary fiber and vitamins (Table 2). The main fatty acids included oleic, linoleic, palmitic and stearic acids in a ratio of 37.7% and 34.8%, 27.4% (Kizil & Turk, 2010).

5. Scientific-based effects of sumac

As discussed previously, MetS including diabetes mellitus, dyslipidemia, cancer and cardiovascular diseases, have become a common health problem in both developed and developing countries (Wang, Lee, Liu, Portincasa, & Wang, 2020). Accumulating data have suggested that traditional herbs might be able to provide a wide range of remedies in prevention and treatment of metabolic disorders. In this context, sumac richness in phytochemicals propounds its uses as medicinal plant against several MetS (Ghafouri et al., 2021). The principal effects of the major compounds present in sumac are reported in Table 3:

And besides its active compounds, effects of sumac on MetS were also investigated at different study levels. Cellular and animal studies (Table 4), and human studies (Table 5) documented that sumac ameliorate hyperlipidemia, hyperglycemia, oxidative stress, and

Table 3
Effects of bio-active components of sumac against metabolic syndrome.

Active compound	MetS	Type of study	references
Gallic acid	Diabetes	Clinical trials, animal, cellular	(Ferk et al., 2018) (Variya, Bakrania, & Patel, 2020) (Gandhi et al., 2014)
	NAFLD	Animal	(Sousa et al., 2020) (Chao et al., 2014)
	Obesity	Animal, cellular	(Bak et al., 2013) (Tanaka, Sugama, et al., 2020) (Paraiso et al., 2019) (Doan et al., 2015)
	Oxidative-inflammatory damage	Animal	(Diaz et al., 2020) (Singla, Dharwal, & Naura, 2020) (Liu et al., 2020)
Methyl gallate	Oxidative-inflammatory damage	Animal	(Ahmed, Satyam, Shetty, & D'Souza, 2021) (Correa et al., 2020) (Reyes et al., 2016)
	Cancer	Animal, cellular	(Kim et al., 2016) (Lee et al., 2010) (Lee et al., 2013)
	Obesity	Cellular	(Jeon, Rahman, & Kim, 2016)
Quercetin	Obesity, hypertension	Clinical trials	(Nishimura, Muro, Kobori, & Nishihira, 2019) (Egert, Boesch-Saadatmandi, Wolffram, Rimbach, & Muller, 2010) (Brull et al., 2015) (Egert et al., 2009)
Myricetin	Obesity, NAFLD	Animal	(Hu et al., 2018) (Nallappan, Ong, Palanisamy, Chua, & Kuppusamy, 2020) (Su, Feng, Zheng, & Chen, 2016) (Sun et al., 2021) (Xia et al., 2019) (Xia et al., 2016)
Cyanidin, delphinidin	Obesity, NAFLD, Diabetes, Inflammation	Animal	(Gharib, Faezizadeh, & Godarzee, 2013) (Daveri et al., 2018) (Huang, Zhao, Xia, & Shen, 2020) (Kawk et al., 2020) (Zhou et al., 2020) (Wei et al., 2011) (Li, Shi, et al., 2020)

inflammation.

5.1. Cellular and animal studies

5.1.1. Diabetes

Several studies conducted *in vitro* and *in vivo* have showed that sumac (*R. coriaria*) possess promising antidiabetic potentials. In fact, a study using non-insulin-dependent diabetes mellitus rats, revealed that treatment with *R. coriaria* reduced the levels of blood glucose, glycated hemoglobin A1c (HbA1c) and insulin with a significant improvement in glucose tolerance (Anwer et al., 2013). Two other studies (Ahangarpour et al., 2017; Dogan & Celik, 2016) as well investigated the 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 total cholesterol (TC) and triglycerides (TG) (Ahangarpour et al., 2017; Doğan & Çelik, 2016). While in Alloxan-induced diabetic rats, administration of the extract of *R. coriaria* fruits produced a statistically significant acute and long-term decrease in postprandial blood glucose concentration. Furthermore, *R. coriaria* affected both cholesterol levels and antioxidant activities. It increased markedly HDL level and reduced LDL and it had noticeable antioxidant effects by elevating superoxide dismutase (SOD) and catalase (CAT) activities (Mohammadi, Montasser Kouhsari, & Monavar Feshani, 2010). Besides the blood glucose reduction, sumac treatment also reduced the liver and kidney tissue contents of malondialdehyde in diabetic group (Salimi et al., 2015).

In other diabetic animal models, which also diabetic complications may occur, such as dyslipidemia, liver injury and even reproductive complications, treatment with sumac showed marked beneficial effects. In details, aqueous extracts of sumac alone or in combination with other medicinal plants led to significant decreases in the levels of alkaline phosphatase (ALP), low-density lipoprotein cholesterol (LDL-C) and blood glucose (Abedi Gaballu et al., 2015). In addition, *R. coriaria* decreased the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, alkaline phosphatase, creatinine and urea in the diabetic group, showing possible hepato- and renal protective effects. Whereas in nicotinamide-streptozotocin induced type-2 diabetes in male mice, reproductive disorders such as alteration of body and testicular weight, sperm count and viability, and serum luteinizing hormone, follicle-stimulating hormone and testosterone levels were occurred in diabetic mice. The administration of hydro-Alcoholic Extract of sumac was able to recover male mice from these reductions (Ahangarpour, Oroojan, Heidari, Ehsan, & Rashidi Nooshabadi, 2014). *R. coriaria* showed also an α-amylase, α-glucosidase, and pancreatic lipase inhibitory activities (Giancarlo, Rosa, Nadjafi, & Francesco, 2006; Gok, Deliorman Orhan, Gurbuz, & Aslan, 2020).

Taken together, these studies demonstrate that *R. coriaria* could be effective against diabetes and useful for alleviation of diabetes complications such as hypolipidemic, liver and renal damage and male infertility.

5.1.2. Inflammation

The anti-inflammatory properties of sumac have been known and valued for decades. During the past decades, many studies have provided scientific support for the long-held belief that sumac is effective against inflammation and inflammation-related diseases. Sumac showed a beneficial effect for the prevention and treatment of necrotizing enterocolitis (NEC). Using a rat model for NEC causing intestinal damage, the anti-inflammatory, antioxidant, immunomodulatory, and anti-apoptotic activities of sumac were demonstrated. This suggests sumac as a promising treatment option for preventing intestinal tissue damage (Isik et al., 2019). Other study has evaluated the antioxidative, modulative of inflammatory cytokines, and apoptotic genes properties of sumac extract administration on morphine-induced fertility destruction in male Wistar rats. It was revealed that sumac application reduced p53 and caspase-3 genes expression 2 markers of apoptosis, and inflammatory cytokine whereas it improved sperm parameters, total antioxidant capacity (TAC), testosterone, and germinal layer height (Roshankhah, Gholami, & Salahshoor, 2020).

The inflammatory cytokines modulation effect of sumac was also tested in Lipopolysaccharide LPS-stimulated synoviocyte cells. The expression of IL-18, IL-1β genes in the articular joint was reduced by sumac fruit extract (Momeni, Maghsoodi, Rezapour, Shiravand, & Mardani, 2019). In addition, *R. coriaria* extracts inhibited or slowed down the progress of skeletal muscle atrophy by decreasing oxidative stress via superoxide dismutase 2 and catalase-dependent mechanisms (Najjar et al., 2017). Other studies were designed to explore the analgesic effects of sumac in acetic acid-induced contractions in rats. *R. coriaria* extract significantly inhibited the number of contractions and showed an anti-nociceptive activity (Mohammadi, Zarei, Zarei, & Salehi, 2016) (Mohammadi, Zarei, & Zarei, 2015). Such effect on muscle contraction raised the question about its effectiveness during aerobic exercise. Indeed, sumac juice consumption was able to ameliorate and

Table 4
Main studies *in vitro* (cellular models) and *in vivo* (animal models) of Sumac.

Author	Study type	Disease	Experimental model	Sample used	Main outcomes
(Anwer et al., 2013)	Animal	Diabetes	Rats	Extract	↓Blood glucose, HbA1c, insulin
(Dogan & Celik, 2016)	Animal	Diabetes, Liver damage	Streptozotocin (STZ)-induced diabetic rats	Extract	↓Blood glucose ↓TG, TC ↓AST, ALT, LDH, ALP
(Ahangarpour et al., 2017)					
(Mohammadi et al., 2010)	Animal	Diabetes	*Rats*	Extract	↓Blood glucose ↑HDL ↓LDL ↑SOD, CAT ↓maltase and sucrase activities.
(Salimi et al., 2015)	Animal	Diabetes	male Wistar rats	Extract	↓Blood glucose ↓MDA ↑CAT
(Ahangarpour et al., 2014)	Animal	Diabetes	male mice	Extract	↑Body and testicular weight, sperm count and viability, serum luteinizing hormone, follicle-stimulating hormone and testosterone levels.
(Abedi Gaballu et al., 2015)	Animal	Diabetes	Rats	Extract	↓ ALP, LDL-C, creatinine, blood glucose
(Isik et al., 2019)	Animal	Necrotizing enterocolitis	Newborn Rat NEC model	Powder	↓MDA, DNA/protein oxidation ↓Apoptosis
(Nozza et al., 2020)	Cellular	skin injuries	microvascular endothelial cells (HMEC-1)	Extract	↓ROS Production ↓DNA lesions
(Khalilpour et al., 2019)	Cellular	skin injuries-Inflammation	human keratinocytes (HaCaT cells*)*	Extract	↓IL-8 release ↓NF-κB activation, ICAM-1, and MMP-9 secretion
(Roshankhah et al., 2020)	Animal	male fertility-inflammation	male Wistar rats	Extract	↓P53, caspase-3, inflammatory cytokine ↑total antioxidant capacity (TAC), testosterone
(Gabr & Alghadir, 2019)	Animal	Skin wound tissues	Wistar male rats	Extract	↓Wound area, ↑Deposition of collagen, HPX ↓MMP-8, and MPO enzyme
(Najjar et al., 2017)	Cellular/ Animal	Oxidative stress	human myoblasts/ *:* zebrafish embryos	Extract	↑SOD, CAT ↓ROS production ↓Cell death
(Momeni et al., 2019)	Cellular	Osteoarthritis	LPS-induced synoviocyte cells	Extract	↓IL-18, IL-1β
(Saglam et al., 2015)	Animal	periodontitis	Wistar male rats	Extract	↓Alveolar bone loss ↓Inflammatory cell infiltrate ↓RANKL-positive cells ↑OPG-positive cells ↓Oxidative stress
(Mohammadi et al., 2016)	Animal	Pain	male rats	Extract	↓Number of contractions ↑Anti-nociceptive activity
(Khalil et al., 2021)	Cellular	Neuro-inflammation	Microglia cells (BV-2)	Extract	↓ROS production, NO release ↓TNFα, iNOS, COX-2 ↓NF-κβ activation ↑IL-10
(Khalilpour et al., 2018)	Animal	Neuro-inflammation	albino Balb/c mice	Extract	↓Ocular ischemia
(Ghaeni Pasavei et al., 2021)	Animal	Hepatic steatosis	HFD-male Wistar rats	Extract	↓TG, TC, MDA
(Pourahmad et al., 2010)	Cellular	Liver injury	Rat hepatocyes	Extract & Gallic acid	↓MDA, membrane lysis and ROS generation
(Ahmadian et al., 2020)	Animal	Growth performance-obesity-immunity	Male Ross broiler chicks	Powder	↓Feed intake ↓Abdominal fat ↓ LDL ↓Blood glucose ↑Antibody titers to Newcastle disease and influenza
(Azizi et al., 2020)	Animal	Growth performance-obesity-immunity	one day-old male broilers	Powder	↓TC, LDL ↑HDL ↓*E. coli* count in broiler ileal
(Gurbuz & Salih, 2017)	Animal	Hypercholesterolemia	laying hens	Powder	↓Egg yolk/blood cholesterol
(Shafiei et al., 2011)	Animal	Hyperlipidemia	male Wistar rats	Extract	↓TC, TG, AST, ALT, LDH ↓Hypertrophic cardiac histology
(Capcarova et al., 2012)	Animal	Hypercholesterolemia	male rabbits	Powder	↑Platelet distribution width) ↓TC ↑total antioxidant status

(*continued on next page*)

Table 4 (*continued*)

Author	Study type	Disease	Experimental model	Sample used	Main outcomes
(Chao et al., 2014)	Animal	NAFLD-Obesity	HFD male C57BL/6 mice	Gallic acid	↓Body weight ↓Insulin resistance ↓TG, TC, AAT, ALT ↓Liver lipid accumulation
(Tanaka, Sato, et al., 2020)	Cellular	NASH	palmitic acid (PA)-induced steatosis in HepG2 cells/ co-colture hepatocyte-macrophage crosstalk	Gallic Acid	↓Fat accumulation ↑ AMPK ↓Cell injury and apoptosis ↓Inflammatory mediator expression ↑ Antioxidant enzyme expression.
(Farag et al., 2020)	Cellular	Microbiota	*Bacterial microbita culture*	Extract	↑SCFA ↑Fructose
(Anwar et al., 2018)	Animal	CVD	Male Sprague-DawleyRats	Extract	↑ Relaxe rat isolated aorta. ↑NO production and cGMP ↑PI3K-Akt.
(Beretta et al., 2009)	Animal	ischemia	isolated rabbit heart and thoracic aorta	hydrolysable gallotannins from extract	↓Coronary perfusion pressure ↓Left ventricular contracture ↑Left ventricular developed pressure ↓Creatinine kinase, LDH ↑ 6-ketoprostaglandin F ↓TNF-alpha endothelium-dependent vasorelaxation
(Kubatka et al., 2020)	Animal	Breast Cancer	Female Sprague-Dawley rats/ Female BALB/c mice	Powder	↓Tumor volume. ↓Mitotic activity index. ↑Caspase-3, Bax/Bcl-2 ↓Bcl-2, Ki67, CD24, ALDH1, EpCam ↓Lysine methylation status of H3K4m3 and H3K9m3. ↑Lysine acetylation in H4K16ac levels. ↓Oncogenic miR210 ↑Tumor-suppressive miR145.
(El Hasasna et al., 2016)	Cellular /Animal	Breast cancer	MDA-MB-231cells/chick embryo	Extract	↓Migration and invasion ↓MMP-9, prostaglandin E2 (PgE2) ↓Angiogenesis,VEGF production ↓TNF-α, IL-6 and IL-8 ↓NFκB, STAT3, NO ↓Tumor growth and metastasis *in vivo.*
(El Hasasna et al., 2015)	Cellular	Breast cancer	Breast cancer cell lines	Extract	↓Proliferation ↑Cell cycle arrest ↑Apoptosis ↑p38 and ERK1/2 ↑Autophagy ↑Senescence
(Athamneh et al., 2017)	Cellular	Colon cancer	HT-29 and Caco-2 human colorectal cancer cells	Extract	↓Viability and colony growth. ↑Beclin-1-independent autophagy ↑Caspase-7-dependent apoptosis. ↓AKT/mTOR ↑Proteasome-dependent degradation. ↑Beclin-1, p53 and procaspase-3 ↑Degradation of mTOR
(Mirian et al., 2015)	Cellular	Angiogenesis	HUVEC and Y79 cell lines	Extract	↑ Cytotoxic effect in cancer cells ↓Tube formation

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; HbA1c, glycated haemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; HFD, Hight 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; NFκB, nuclear factor kappa B; PPARγ, peroxisome proliferator-activated receptor-γ; 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-α, serum levels of tumor necrosis factor.

the reduce muscle pain (Alghadir & Gabr, 2016). These encouraging results on muscle performance propose sumac administration as an effective medication for reducing muscle pain.

In different aspects, Sağlam et al. evaluated the effect of sumac in suppressing periodontal inflammation and alveolar bone destruction in periodontal disease. The study investigates the effects of systemic sumac extract administration on alveolar bone loss by evaluating the changes in RANKL/OPG balance and serum oxidative status in experimental rat periodontitis. Sumac significantly reduced total oxidant status (TOS), and oxidative stress index (OSI) levels and reduced alveolar bone loss and RANKL expression (Saglam, Koseoglu, Hatipoglu, Esen, & Koksal, 2015).

Sumac has showed also a wound healing capacity via promoting myofibroblast activity, increasing of hydroxyproline and collagen deposition, and regulation of MMP-8 and MPO enzyme activities (Gabr & Alghadir, 2019). Therefore, sumac had a preventive effect against keratinocyte inflammation through their inhibitory effect on the production of skin pro-inflammatory mediators (Khalilpour et al., 2019). The protective effect of sumac was also determined *in vitro* against UV-A-induced genotoxicity and oxidative damage in human microvascular endothelial cells (Nozza et al., 2020) and *in vivo* against urethane-induced genotoxicity rat bone marrow cells (Timocin, Arslan, & Basri

Table 5
Main clinical controlled trials involving intake of "Sumac".

Authors	N. of subjects	Gender (Age)	Participants	Formulation, posology	Duration of study	Main findings
(Hajmohammadi et al., 2018)	80	Men and women (20–65 years)	hyperlipidemic subjects	500 mg of sumac capsules twice per day	42 days	↓HDL-C ↓ Apo-A1
(Hajmohammadi et al., 2016)	80		hyperlipidemic subjects	1000 mg/day	60 days	↑HDL cholesterol level
(Asgary et al., 2018)	30	Men and women (35–65 years)	hyperlipidemic subjects	500 mg of sumac capsules twice per day	28 days/ 14 days washout/ 28 days placebo	↓BMI ↓Systolic and diastolic BP ↓Total-C ↓LDL-C ↑FMD
(Sabzghabaee et al., 2014)	72	Men and women 12–18 years	Obese adolescents	500 mg of sumac capsules three time per day	28 days	↓TC ↓LDL-C ↓TG
(Kazemi et al., 2020)	84		NAFLD	2000 mg per day sumac powder	84 days	↓Hepatic fibrosis ↓ ALT, AST ↓FBS, serum insulin ↓HbA1c ↓HOMA-IR ↓MDA ↓hs-CRP ↑QUICKI
(Hariri et al., 2020)	62	obese women aged 20–65	Obesity	3 g/day	12 weeks	↓BMI, body fat, visceral fat, MDA
(Rahideh et al., 2014)	41		Diabetes	3 g/day	3 months	↑Paraoxonase 1 ↓Insulin, insulin resistance, MDA, hs-CRP
(Shidfar et al., 2014)	41		Diabetes	3 g/day	3 months	↓Glucose, HbA1c, apoB ↑ApoA-I, total antioxidant capacity
(Alghadir & Gabr, 2016)	40	healthy volunteers	muscle Pain	*Rhus coriaria* (sumac) juice	30 days	↓Pain score during exercise and post-exercise ↑Creatine kinase, LDH, troponin I, hydroxyproline

Abbreviations: ↓, significantly decreased; ↑, significantly increased; BP, blood pressure; BMI: Body mass index; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TC, total cholesterol; TBARS, thiobarbituric acid-reactive substances; HbA1c, glycated haemoglobin A1c; ICAM, intracellular adhesion molecule; FMD, flow-mediated dilatation; GPX, glutathione peroxidase; SOD, superoxide dismutase; TG, triglycerides; AIP, atherogenic index plasma; KOOS, knee injury and osteoarthritis outcome score; TUG, timed up and go; MDA, malondialdehyde; TAC, total antioxidant capacity; BMI, body mass index; SHBG, serum sex hormone–binding globulin; 2-OHE1, urinary 2-hydroxyestrone; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; hs-CRP, high-sensitivity C-reactive protein; LDH: lactic acid dehydrogenase.

Ila, 2019). In both model, sumac showed an antioxidant and anti-inflammatory properties.

5.1.3. Neuroprotective effects

The neuroprotective effect of sumac was also investigated by our previous study (Khalil et al., 2021) using an *in vitro* cellular model of neuro-inflammation, the sumac extract exerted a potent anti-inflammatory potential on insulted BV-2 cells manifested by inhibition of reactive oxygen species (ROS) production and nitric oxide (NO) release; suppressing TNFα, iNOS and COX-2 mRNA levels; reducing NFκβ activation; and enhancing IL-10 transcription levels. In addition to *in vitro* investigation, *in vivo* study using mouse model of ischemic optic neuropathy also showed a neuroprotective and anti-inflammatory effects of sumac treatment (Khalilpour et al., 2018). These findings suggest that *R. coriaria* might carry therapeutic potential against neuro-inflammation and neurodegenerative diseases.

5.1.4. Liver, obesity, and gastrointestinal disorders

Pourahmad et al. evaluated the hepato-protective effects of *R. coriaria* and its main component gallic acid against hydroperoxide-induced oxidative stress and toxicity in isolated rat hepatocytes. Aqueous extracts of *R. coriaria* were effective in reducing lipid peroxidation, ROS production and hepatocyte membrane lysis (Pourahmad, Eskandari, Shakibaei, & Kamalinejad, 2010).

In vitro inhibitory effect of urease enzyme was also tested; urease enzyme has a crucial role in the persistent habitation of *Helicobacter pylori* that induces gastrointestinal diseases, in particular gastritis, duodenal, peptic ulcer, and gastric cancer. In this study, sumac showed a potent inhibitory effect against Jack bean urease activity (Mahernia, Bagherzadeh, Mojab, & Amanlou, 2015).

Multiple experimental studies have shown the anti-obesity and anti-hyperlipidemic effects of sumac in animal models. For example, *R. coriaria* improved hepatic steatosis and dyslipedimia in high-fat diet rats. In details, the levels in the serum lipid profile (TG, cholesterol, HDL, LDL and MDA) in rats fed with the high fat diet (HFD) and then treated with sumac were significantly reduced (Ghaeni Pasavei et al., 2021). In rabbits, sumac led to a significant increase in PDWc (platelet distribution width) and decreased cholesterol levels (Capcarova et al., 2012). In rats fed with high cholesterol diet, Shafiei et al. showed that sumac fruit extract alleviates the lipid abnormalities by reducing the levels of TC and TG along with augmented activities of serum aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase and also reversed the hypertrophic cardiac histology confirming that sumac possesses cardioprotective and hepatoprotective activities which will be beneficial in hypercholesterolemic condition (Shafiei, Nobakht, & Moazzam, 2011).

In Ross broiler chicks, sumac supplements reduced feed intake, body weight and abdominal fat, as well as blood glucose level with little effect of the supplements on carcass composition (Ahmadian, Seidavi, & Phillips, 2020). In the contrary, a second study indicated that supplementing sumac powder had no effect on broiler body weight gain, feed intake and feed conversion as well as carcass characteristics. Conversely, serum total cholesterol and LDL-cholesterol levels were decreased, while HDL-cholesterol increased in all sumac powder fed groups compared to control, Moreover, the lactobacilli count remained unaffected by dietary treatments, while E. coli count in broiler ileal content was lower when fed with sumac powder which indicates that sumac has significant antimicrobial activity that can reduce the pathogenic bacteria in gut tract (Azizi et al., 2020). Similarly, feeding sumac to laying hens decreases cholesterol levels in both yolk and blood (Gurbuz & Salih, 2017). Taken together, the findings of these studies introduce sumac as a future potential protective agent in poultry production.

5.1.5. Gut microbiome

The impact of Sumac on microbiota was evaluated using *in vitro* model of gut microbiota by assessing in a whole by untargeted metabolomics. Farag et al. investigated in detail the response of the gut microbiota to sumac and other potential functional food treatment. After an incubation period, microbiota bacterial growth samples were aliquoted and analyzed using GC–MS to reveal any metabolite changes occurring in culture. A general decrease in amino acid levels and nitrogenous compounds was observed. Interestingly, a significant decrease in sugar levels is observed also in sumac treated samples. In contrast, a 2-fold increase in short-chain fatty acids (SCFA) levels and nucleic acids was observed upon incubation with sumac. This study demonstrated the metabolic pathways adopted by microbiota in the generation of SCFA through either nitrogen metabolism of amino acids or carbon metabolism of sugars lead to an ultimate increase of SCFA under consumption of sumac (Farag et al., 2020). In addition, gallic acid (GA), which is the most abundant phenolic compound in sumac, modulated the rat microbiota composition by increasing the probiotic bacteria, such as *Lactobacillaceae* and *Prevotellaceae,* and decreasing some pathogenic species, mainly in the Firmicutes and Proteobacteria. GA also induced metabolic changes by increasing carbohydrate bile acid metabolism and decreasing amino acid metabolism (Li et al., 2019). Additionally, gallic acid-rich plant extracts showed a potential prebiotic effect associated with reduction of intestinal inflammation and promotion of intestinal integrity (Kim et al., 2021).

5.1.6. Cardiovascular diseases

In the cardiovascular systems, accumulating evidence suggest that sumac exhibits multiple and health-promoting cardiovascular effects. The vasorelaxant effect of sumac was investigated in isolated rat aorta, which showed a relaxing action. The mechanistic effect is achieved via stimulation of multiple transducers namely PI3-K/Akt, eNOS, NO, guanylyl cyclase, cGMP, and PKG. Interestingly, the arachidonic acid pathway (cyclooxygenases), adenylyl cyclase/cAMP and ATP-dependent potassium channels appear to partake in this sumac-orchestrated attenuation of vascular tone (Anwar, Samaha, Baydoun, Iratni, & Eid, 2018). Similarly, the cardioprotective effect sumac was additionally evaluated in isolated rabbit heart preparations submitted to low-flow ischemia/reperfusion damage. As results, the hydrolysable gallotannins extracted from sumac leaves (which also presents in Sumac fruits), induces an endothelium-dependent normalization of coronary perfusion pressure (CPP), reducing left ventricular contracture during ischemia, and improving left ventricular developed pressure. Plus, creatinine kinase (CK) and lactate dehydrogenase (LDH) enzymes were significantly reduced during reperfusion. These effects seem to be attributed to the release of the cytoprotective 6-ketoprostaglandin F (1alpha) (6-keto-PGF (1alpha)) and a decrease of tumor necrosis factor-alpha (TNF-alpha) modulating the coronary endothelium cyclooxygenase (COX) pathway. The cardiovascular protective effect of *R. coriaria* seems to be due to interplay of different factors (Beretta, Rossoni, Santagati, & Facino, 2009).

5.1.7. Cancer

Multiple reports have provided strong evidence that sumac suppress tumor growth and survival (Mirian, Behrooeian, Ghanadian, Dana, & Sadeghi-Aliabadi, 2015). The anti-breast cancer activity was evaluated in different breast cancer cell lines, sumac induced senescence and autophagic cell death, (El Hasasna et al., 2015), suppress migration, invasion, metastasis and tumor growth, these finding were also confirmed *in vivo* using chick embryo tumor growth assay (El Hasasna et al., 2016). The underlying mechanism for *R. coriaria* effects appears to be through inhibiting NFκB, STAT3 and NO pathways. In addition, sumac demonstrates oncostatic activity in the therapeutic and preventive model of breast carcinoma. In this regard, 2 *in vivo* models were used: mice 4T1 adenocarcinoma allograft model and chemically-induced rat mammary carcinogenesis model. Interestingly, sumac induced significant chemopreventive and therapeutic efficacy in both animal models, including proapoptotic, antiproliferative, anti-angiogenic and epigenetic changes (Kubatka et al., 2020).

In parallel, the anticancer potential of sumac was also investigated on HT-29 and Caco-2 human colorectal cancer cells. Treatment with sumac extract significantly inhibited the viability and colony growth of colon cancer cells. Moreover, sumac treatment induced Beclin-1-independent autophagy and subsequent caspase-7-dependent apoptosis. In addition, sumac was able to inactivate the AKT/mTOR pathway by promoting the proteasome-dependent degradation of both proteins (Athamneh et al., 2017).

5.2. Human studies

The therapeutic potential of sumac has been studied and evaluated in scientific circles including *in vitro* and *in vivo* studies. Interestedly, Sumac has also reached the stage of clinical trials in humans. The lipid-lowering, antidiabetic, and anti-inflammatory effects of *R. coriaria* have been investigated in different human studies (Table 5). It starts when Sabzghabaee et al. investigated the clinical effects of sumac fruits on dyslipidemia in 12–18 years-old adolescents using randomized triple-blinded clinical trial, after one month trial, *R. coriaria* reduced the serum levels of TC, LDL-C, and TG (Sabzghabaee, Kelishadi, Golshiri, Ghannadi, & Badri, 2014). In 2018, 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). These finding were in accordance with another trials that showed a significant HDL cholesterol increasing effect of sumac supplementation in patients with hyperlipidemia (Hajmohammadi et al., 2016).

During the same year, another study 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 of blood pressure, serum TC and LDL, non-HDL-C, and BMI was observed in the sumac group compared to placebo group (Asgary et al., 2018).

The antidiabetic potential of sumac was also investigated using a double-blind randomized placebo-controlled trial on 41 type 2 diabetic volunteers. Consumption of 3 g per day sumac powder led to a significant increase in paraoxonase 1 (PON1) activity, and decrease in insulin resistance (IR), malondialdehyde (MDA), high sensitive C-reactive protein (hs-CRP). In addition, there were significant decreases in serum glucose and HbA1c and also apoB levels and a significant increase in apoA-I (Rahideh et al., 2014; Shidfar et al., 2014).

More recent, the beneficial effects of sumac supplementation on obesity management and NAFLD were also investigated. Sumac supplementation along with restricted calorie diet in overweight or obese women with depression significantly reduced weight, BMI, body fat, visceral fat level and malondialdehyde levels, in comparison with the placebo group (Hariri et al., 2020).

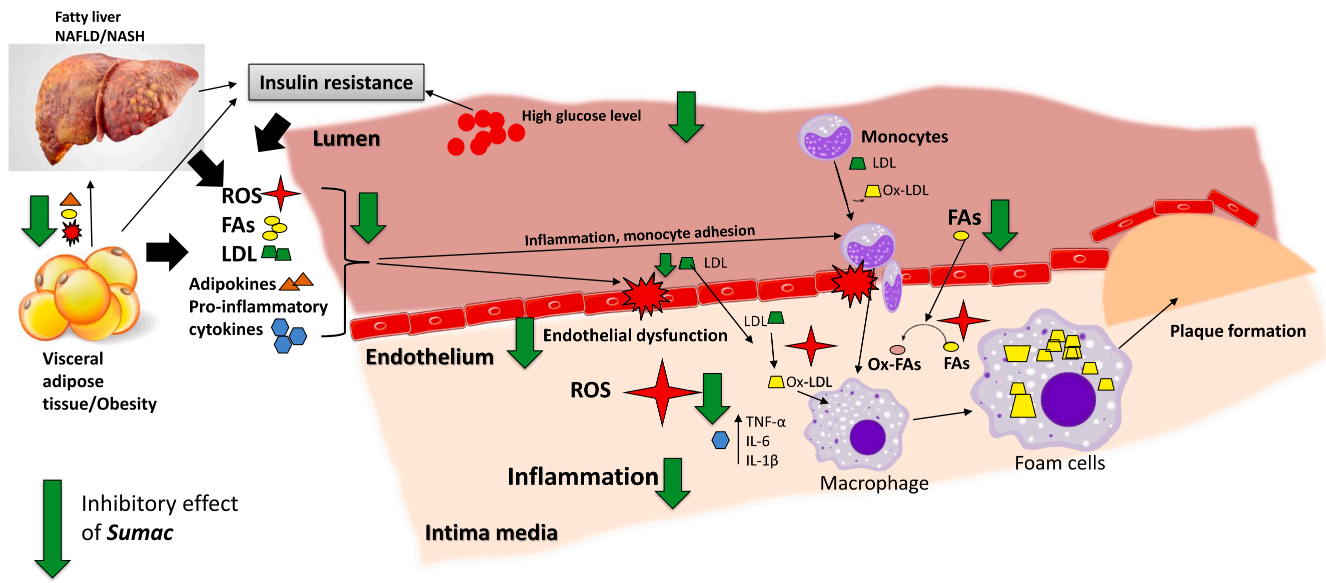

Fig. 5. Overall effect of sumac against the most MetS hallmarks in NAFLD/obesity-induced atherosclerosis.

In NAFLD research, 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, HbA1c, 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 in 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 since they are well recognized for their antioxidant, anti-inflammatory and hepatoprotective activities. However, no evidence exists so far for chemopreventive or anti-tumor effects of sumac in humans.

6. Summary

Atherosclerosis, one of the primary causes of CVDs, is a vascular disease that occurs at susceptible sites in major arteries. It is an inflammatory process and ultimately causes stenosis or thrombosis with potentially lethal distal ischemia. A myriad of risk factors are involved in the complex pathogenesis of atherosclerosis include hyperlipidemia and endothelial injury. In the same context, many of NAFLD patients showed many atherosclerosis-related risk factors such as endothelial dysfunction, inflammation, and hyperlipidemia. Therefore, the association of these two diseases with metabolic disorders was a center of attention in order to investigate the lane that orient NAFLD patient towards developing atherosclerosis.

In the other hand, herbs and medicinal plants as well as functional food contain vast collections of biologically active compounds, especially polyphenols, with multiple mechanisms of action that may potentiate each other's activity or have a synergistic effect, providing greater benefit than a single chemical agent. The term "pharmacodynamic synergy", describe the synergy effect between different substances in plant extracts which can act at different receptor targets involved in the MetS to enhance the overall therapeutic effect (Rasoanaivo, Wright, Willcox, & Gilbert, 2011). In fact, such effect has been documented for many pharmacological activities where compounds with little/no activity or present in low concentration can assist and modulate the main active compounds to reach the target by improving bioavailability, or by decreasing metabolism and excretion (Williamson, 2001). In addition, other compounds can interact as complementary mechanisms of action, reversal of resistance, and modulation of adverse effects. Taken together, the multi-functionality and the pharmacodynamic synergy of medicinal plants may serve as effective approach for the treatment or prevention of MetS (Graf, Raskin, Cefalu, & Ribnicky, 2010) where the complexity of the MetS may be addressed with a treatment or prophylactic strategy involving these complex compounds.

Flora of the Mediterranean area includes many edible species that have been used in traditional medicine and have always represented an important source of bioactive compounds. In the Mediterranean basin, folk medicine is widely diffuse, and the region is rich in medicinal plants. Sumac, *R. coriaria*, is a wild edible plant growing in the Mediterranean region. The dried fruits are the most commonly consumed part of this plant which is typically used as a condiment, spice, sauce, and appetizer. In folk medicine, sumac plant has been used in the treatment of many disorders; it is rich in phenolic compounds (PC), especially hydrosoluble tannins and flavonoids with vast range of biological and pharmacological activities.

These qualities of sumac plant promoted its early uses in traditional medicine. However, results from different studies conducted not only in cellular and animal models, but also in humans could "evoque" its importance in modern medicine. 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. In this context, sumac could have a direct impact on human health and could promote potentials pharmacological effects, in particular for metabolic disorders such as NAFLD and cardiovascular and peripheral vascular diseases by regulating MetS involved. In this respect, additional and profound studies are still required.

Regarding the beneficial properties of Sumac, in the treatment/ prevention of MetS especially in the scenario of NAFLD-atherosclerosis interaction where different risk factors are involved such as dyslipidemia, diabetes, and obesity (Fig. 5), in Tables 4 and 5, different cellular, animal, and human studies have been discussed suggesting that sumac could be a potential nutraceutical/ therapeutic candidate in the therapy of MetS. Sumac had a notable efficacy on increasing HDL and decreasing TG, LDL, and TC levels. Results also showed that sumac significantly reduced fasting glucose, HbA1c, and insulin resistance through different mechanisms including antioxidant, anti-inflammatory, cytoprotective, increasing insulin sensitivity. Human studies showed that Sumac is also able to reduce body fat accumulation and visceral fats decreasing body weight in obese people. These effects were concomitant with potential anti-inflammatory proprieties including reduction of MDA level as well as hs-CRP level. Some animal and human studies reported the antihypertensive effect of sumac whish also was able to relax rat isolated aorta through NO production and cGMP and PI3K-Akt signaling pathway. Furthermore, sumac showed a potential role in ameliorating liver injury and fatty liver diseases, in particular, sumac was able to reduce the steatosis and fibrosis rate, as well as rescue the fat-dependent inflammation and oxidative stress, in addition, sumac reduced the liver enzymes level in NAFLD patients. Finally, since MetS are strictly linked to cancer, and sumac has beneficial effects on obesity and MestS, its uses may decrease the risk factors of several tumors including breast cancer and colorectal cancer.

Taken together, the reported beneficial effect of sumac against the most MetS hallmarks, suggest that sumac could be effective in NAFLD-induced cardiovascular diseases such as atherosclerosis through its antioxidant, anti-inflammatory and hypolipidemic effects.

7. Future perspectives and conclusion

Describing and examining sumac's data collection, it can be concluded that *R. coriaria* contains valuable biologically active components, such as polyphenols which may be responsible for their biological effects with considerable antioxidant and anti-inflammatory abilities. In summary, based on our review, the daily intake of sumac may assist in the treatment and/or prevention of metabolic syndrome and its related diseases such as NAFLD, inflammation, cancer and atherosclerosis. Despite the well-studied beneficial effects of Sumac on human health, information about the interaction with gut microbiota and intestinal permeability and absorption are still lacking so far. Thus, studying gut microbiota is fundamental, since gut-food interaction is the key player in functional food-mediated bioactivity. In this regard, our future investigation will address this aspect of great interest.

Funding

The present work is written in the context of the project FOIE GRAS, which has received funding from the European Union's Horizon 2020 Research and Innovation framework, under the Marie Skłodowska-Curie Grant Agreement No. 722619 (P.P.) and the mitoFOIE GRAS funded by H2020-MSCA-RISE-2016/H2020-MSCA-RISE-2016 Grant Agreement No. 734719 (P.P.), and the project SYSTEMIC which has received funding from national research funding parties in a joint action of JPI HDHL, JPI-OCEANS and FACCE-JPI launched in 2019 under the ERA-NET ERA-HDHL (n° 696295).

Ethics statement

Our review did not include any human subjects and animal experiments.

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.

Acknowledgements

Authors thank the financial support from project FOIE GRAS and SYSTEMIC. We would like also to thank Dr. Ali al-khatib and Mr. Ali Khalil for providing the traditional books.

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