REVIEW ARTICLE
VOL. 45 | NO. 2 | **MAY - AUGUST 2024** | PP 35-61

Revista Mexicana de Ingeniería Biomédica

dx.doi.org/10.17488/RMIB.45.2.3

E-LOCATION ID: 1410

Salvia rosmarinus Spenn. Main Applications and Ultrasonic Extraction of Secondary Metabolites: a General Review

Salvia rosmarinus Spenn. Principales Aplicaciones y Extracción Ultrasónica de Metabolitos Secundarios: una Revisión General

José Juan Cedillo-Portillo[1], *Wendy Yaneth Villastrigo-López*[1], *Adali Oliva Castañeda-Facio*[1], *Sandra Cecilia Esparza-González*[2], *Elia Martha Múzquiz-Ramos*[1], *Aidé Sáenz-Galindo*[1]

[1]Universidad Autónoma de Coahuila, Facultad de Ciencias Químicas - México

[2]Universidad Autónoma de Coahuila, Facultad de Odontología - México

ABSTRACT

This paper provides an overview of the various applications of the bioactive compounds found in *S. rosmarinus*. at present. Additionally, it explores emerging technologies for its extraction, such as ultrasound, which is an effective, fast, and sustainable technology for obtaining these secondary metabolites from this millenary plant. *S. rosmarinus* has gained considerable importance due to its beneficial properties, including antimicrobial, antioxidant, hepatoprotective, anti-inflammatory, and anticarcinogenic effects. These effects result from the different metabolites, which, without the use of ultrasound, are produced in *S. rosmarinus*. The main objective of this research is to provide an overview of some of the main applications in which *S. rosmarinus* is involved and to present a viable and effective alternative for the extraction of the different metabolites it contains using a technique such as ultrasound. The literature review was performed by searching for information on digital platforms such as SciFinder, PubMed, Scopus, and ScienceDirect, using keywords such as Rosemary, *S. rosmarinus*, ultrasound, green extraction, and secondary metabolite.

KEYWORDS: *S. rosmarinus*, emerging technologies, ultrasound

RESUMEN

En el presente trabajo se muestra un panorama general de las diversas aplicaciones que se tiene hoy en día de los compuestos bioactivos encontrados en *S. rosmarinus* así mismo, se toma en cuenta las tecnologías emergentes para su extracción como el ultrasonido, la cual es una tecnología eficaz, rápida y sustentable para la obtención de estos metabolitos secundarios a partir de esta planta milenaria, dicha planta ha generado una importancia considerable debido a las buenas propiedades que presenta como el efecto antimicrobiano, antioxidante, hepatoprotectora, antiinflamatorio y anticancerígeno, las cuales son productos de los diferentes metabolitos que sintetiza entre los cuales destaca el carnosol, ácido carnósico, rosmadial o rosmanol, ácido rosmarinico entre otros; logrando posicionarla en aplicaciones que van desde el área culinaria hasta aplicaciones dentro de la biomedicina. El objetivo principal de la presente investigación es brindar un panorama general de algunas de las principales aplicaciones en las que se ve involucrado el *S. rosmarinus* y así mismo, dar a conocer una alternativa viable y eficaz para la extracción de los diferentes metabolitos contenidos en este, mediante una técnica como el ultrasonido. La revisión literaria se hizo buscando información en algunas plataformas digitales como Sicfinder, PubMed, Scopus, SiencieDirect, utilizando palabras clave: Rosemary, *S. rosmarinus*, ultrasound, green extraction, secondary metabolite.

PALABRAS CLAVE: *S. rosmarinus*, tecnologías emergentes, ultrasonido

Corresponding author

TO: Aidé Sáens-Galindo

INSTITUTION: Facultad de Ciencias Químicas, Univerdad Autónoma de Coahuila

ADDRESS: Blvd. Venustiano Carranza S/N, República Oriente, C.P. 25280, Saltillo, Coahuila, México.

EMAIL: aidesaenz@uadec.edu.mx

Received:

22 November 2023

Accepted:

22 April 2024

INTRODUCTION

Since prehistoric times, human beings from different cultures have used plants as medicinal sources. Until the 19th century, physicians had used them as the main source of pain relief for their patients. Today, the World Health Organization estimates that about 80 % of people in developing countries still use traditional medicine. Medicinal plants have shown numerous unique and interesting pharmacological properties, including antimicrobial properties[1][2]. Plants synthesize a wide variety of metabolites to protect themselves and maintain homeostasis in their environment. Often, these secondary metabolites differ among plant species in their quantity, diversity, and biological activities[3].

Rosemary (*Rosmarinus officinalis* L. syn *Salvia rosmarinus* Spenn.) is a plant that grows wild in the Mediterranean basin. It is a perennial and aromatic plant belonging to the Lamiaceae family and recently merged with the genus *Salvia*, so it is now known as *Salvia Rosmarinus*[2][4]. It can reach 150 cm in height and is a lush, branched, and evergreen shrub. *S. rosmarinus* is traditionally used as a culinary species to modify or improve food flavors and other organoleptic properties. It is also used in traditional and folk medicine, being a highly valued medicinal herb. About 20 types or varieties of *S. rosmarinus* can be distinguished according to morphological descriptors; however, the infraspecific systematics are confusing and uncertain[5][6].

Currently, *S. rosmarinus* is one of the most important major sources of naturally occurring biologically active compounds in the functional food industry[7][8]. However, this plant possesses many pharmacological activities such as hepatoprotective, antimicrobial, antiulcerogenic, antidiabetic, diuretic, anti-inflammatory, anticarcinogenic, and antioxidant properties. Most of these activities are related to the phenolic content in this shrub. Significantly, the potent antioxidant activity is primarily due to phenolic diterpenes, such as carnosol, carnosic acid, rosmadial, or rosmanol, among others[9].

FIGURE 1. **Specimen of *S. rosmarinus.***

Botanical description

S. rosmarinus. taxonomic series No.: 32677 (ITIS, 2023), belongs to the Lamiaceae family, formerly called Labiatae, and is known by the popular name Rosemary in English, Alecrim in Portuguese, and Romero in Spanish. It is a xeromorphic shrub that grows spontaneously in stony places, sand, cliffs, and sea fences in different parts of the world, such as Europe, Africa, America, and Asia. The shrub is fragrant, with leaves characterized by being strongly curved, linear, and aromatic. The upper part of the leaf has a very intense green hue, while the lower area tends to be gray, with a width of about 4 cm, an average size between 1.0-2.5 cm long, and a thickness ranging from 1-3 mm. The flowers are small and arranged in axillary pauciflorus whorls, light blue, or lilac, both having an intense and fragrant aroma. This aroma is due to the volatile oil accumulated in various parts of the flower, such as the glandular trichomes, petals, and capitate. In Figure 1, the plant of *S. rosmarinus* is presented[10][11].

Chemical composition

The components that confer pharmacological properties to *S. rosmarinus* are classified into flavonoids, terpenoids (sesquiterpenes, triterpenes, diterpenes, monoterpenes), and hydroxycinnamic derivatives[9]. It has been reported that *S. rosmarinus* extracts contain about 24 % of volatile molecules belonging to terpenes, while in the non-volatile fraction, flavonoids appear along with non-volatile terpenoids and phenolic acids. Phytochemical studies have indicated that the concentration of non-volatile compounds varies between 1.8 % and 2.5 %, depending on the region. The predominant constituents are α-pinene, 1,8-cineole, limonene, camphor, and borneol. These differences arise due to the form of cultivation, the growing cycle, and the aging that the plant undergoes at the time of cutting[12][13].

On the other hand, among the most reported chemical compounds in *S. rosmarinus* extracts are rosmarinic acid (RA), chlorogenic acid, caffeic acid, ρ-coumaric acid, carnosic acid (CA), oleanolic acid, betulinic acid, ursolic acid, rosmanol, and carnosol (CR), among other di- and triterpenoids. In such a way, the most involved compounds in various investigations are CA, CR, and AR. This is because these chemical compounds are the main ones responsible for the medicinal activities of the extracts[5][14][15].

The chemical composition of the essential oil of S. rosmarinus has been described in a general way by various researchers who have reported the identification of various chemical molecules such as camphene, α-pinene, and β-pinene, as well as some terpenes like camphor, 1,8-cineole, verbinol, borneol, linalool, rosmanol, terpineol, carnosol, isorosmanol, α-amyrin, β-amyrin, and β-caryophyllene. Additionally, vanillic, chlorogenic, caffeic, ursolic, rosmarinic, carnosic, butylinic, oleanolic, betulinic acids are also identified and different chemical molecules such as botulin, bornyl acetate, 3-octanone, isobanyl-acetate[16].

The different fractions, both volatile and non-volatile, vary greatly depending on the plant due to various factors such as climatic changes, age, region of procurement, and season of the year. Similarly, the concentration of these compounds is not evenly distributed throughout the plant. For example, CA and CR can be found mainly in the photosynthetic tissues of the plant, such as sepals and petals. Several fractions are also significantly affected by the type of processing for the extraction of bioactive compounds. Therefore, the conditions for obtaining these bioactive compounds are crucial, including temperature, type of solvent or extracting agent, and time[9]. Figure 2 shows the structures of some of the chemical compounds present in *S. rosmarinus*.

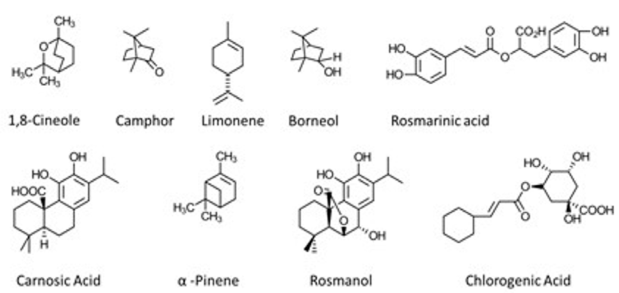


FIGURE 2. Structure of some of the chemical compounds present in *S. rosmarinus.*

Culinary uses

Generally, this plant finds use in Mediterranean cuisine as a condiment contributing flavor to food. The two fundamental ways in which fresh or dried leaves are utilized in the kitchen involve imparting a bitter, astringent, and highly aromatic flavor. Different preparations, such as pork, fish, meat, poultry, soups, stews, dressings, sauces, and various preserves, often see the addition of *S. rosmarinus*. Due to the drying of the leaves, some attributes, like the fresh aroma, are lost. However, the dried leaves gradually lose their quality of life, rendering them highly favorable for storage and transportation. This characteristic transforms them into a profitable product in the market. As a result, the *S. rosmarinus* plant has been employed in the food industry to enhance the shelf life of foods, add value, and improve their quality[14][15].

Food industry

Since ancient times, *S. rosmarinus* has maintained great popularity within the food industry because it contains several bioactive compounds that provide food with antioxidant activity. Some of the compounds responsible include rosmarinic acid, carnosic acid, carnosol, rosmariquinone, rosmanol, and rosmaridiphenol, which can undergo reactions with free radicals formed in oxidation processes. Nowadays, foods containing these types of compounds are of great interest because an increasing number of consumers are opting for foods containing natural antioxidants, considering them to be healthy or "non-chemical"[16][17].

In 2015, the extension of the shelf life and quality of refrigerated fillets of Nile tilapia (*Orechromis niloticus*) by immersing them in a methanolic extract of *S. rosmarinus* at 1.5 % was reported by Khalafalla *et al.*, The result was efficient antioxidant activity with a clear reduction in the value of TBA-RS (a reagent composed of 2-thiobarbituric acid and glacial acetic acid), prolonging the shelf life of these fillets for up to 9 days more than the control[18].

In 2016 in Portugal, a study was reported on the antimicrobial effect provided by the essential oil of *S. rosmarinus* and thyme in foods packaged using the Sous vide cook-chill (SVCC) technology. This technology is characterized by vacuum packaging of raw or partially prepared foods before pasteurization, followed by rapid cooling and storage below 3 °C. In 2016, Gouveia *et al.*, mentioned that at 2 °C, the samples containing thyme essential oil presented a reduction in the population of *L. monocytogenes*; however, it was lower than that observed in *S. rosmarinus* oil. Likewise, the latter managed to show inhibition towards *L. monocytogenes* at a temperature of 8 °C for up to a maximum of 14 days. Furthermore, they highlighted that this dangerous pathogen is found in some "Ready-to-eat" foods and depends on the number of additives present in the food, as well as the temperatures used for storage[19].

In 2016, the antimicrobial Activity against *C. perfringens* of six essential oils usually used as condiments in Brazil (rosemary, basil, marjoram, mint, thyme, and anise) was described by Radaelli. It was pointed out that the use of such oils from commonly employed spices clearly offers an alternative to chemical preservatives for the inactivation and control of pathogens in food. It was also reported that their results suggest that oxygenated compounds, especially monoterpenes and phenylpropanoids, may be responsible for carrying out the antimicrobial Activity. However, a synergistic effect of these chemical compounds with other constituents present in smaller amounts in the essential oil is also considered[20]. The main objective of this research is to provide an overview of *S. rosmarinus*, its main applications, and the implementation of ultrasound extraction for obtaining bioactive compounds present in this plant. This positions this technique as a green and alternative methodology for the extraction of phytochemical compounds.

MATERIALS AND METHODS

The present research was carried out based on a literature search in various databases such as: Scifinder, PubMed, Scopus, ScienceDirect, looking for articles related to *S. rosmarinus*. The search criteria were keywords such as: Rosemary, *S. rosmarinus*, ultrasound, green extraction, secondary metabolite.

RESULTS AND DISCUSSION

Bioactive compounds of plant origin

In nature, unlike animals, plants are stationary and are not exempt from aggressive environmental changes. They are also exposed to harmful microorganisms that become aggressive pathogens, insect pests, parasitic plants, and weeds. This is not to mention temperature changes, mineral and nutrient deficiencies, osmotic imbalance, and contamination by heavy metals. Therefore, plants have a wide range of cellular, molecular, and biochemical protective mechanisms. The metabolic pathways of plants synthesize two types of organic compounds of natural origin or metabolites: (i) primary plant metabolites (PPM), and (ii) secondary plant metabolites (SPM). PPM are produced in large quantities and are responsible for maintaining various vital processes in plants, such as photosynthesis, respiration, growth, and development. Some prominent PPMs include carbohydrates, lipids, proteins, and hormones. They also participate in the primary response by regulating these biomolecules against pathogen infection[12]

In contrast, SPM are produced in minimal quantities, however, they have fundamental functions in plant adaptation to unfavorable conditions. They include various groups of chemical compounds such as alkaloids, flavonoids, anthocyanins, lignans, quinones, peptides, phenols, terpenoids, and amines. These compounds are primarily used in some pesticides, agrochemicals, and food additives. Moreover, they are directly or indirectly related to taste, color, and aroma. Secondary metabolites are synthesized by various pathways in plants and are directly involved in the plant's defensive reaction to an external stimulus[13].

At present, about 200,000 secondary metabolites (MSPs) have been identified, which are divided into four main groups: terpenes, phenols, and nitrogen/sulfur-containing substances. The most important functions of secondary metabolites lie in plant protection[21]. In Figure 3, a classification of the four main groups of secondary metabolites in plants is presented. In Table 1. Main types of the most reported secondary metabolites in the literature for *S. rosmarinus*. as well as their biological activity are presented.

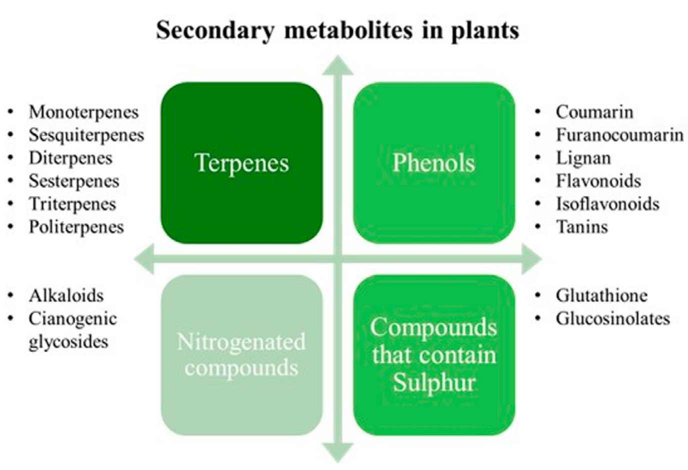
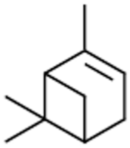
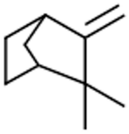
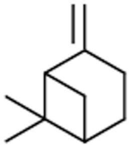
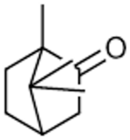
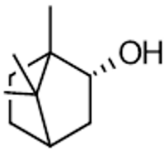
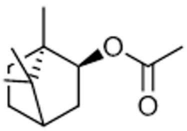
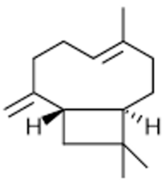
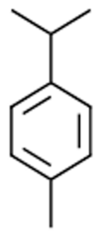
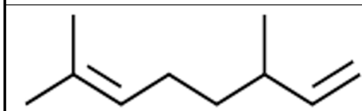
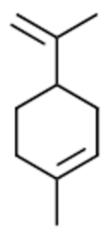
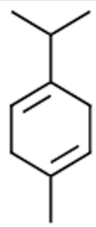
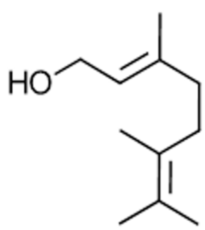
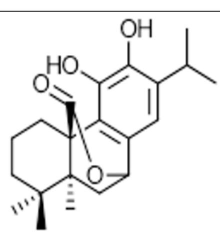
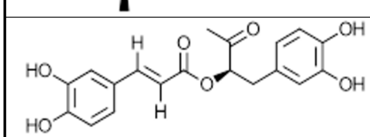
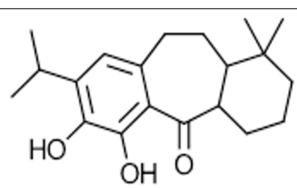
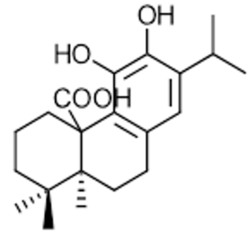
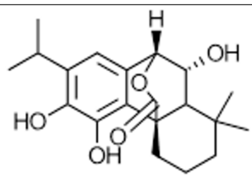
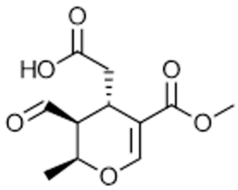
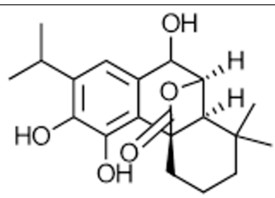
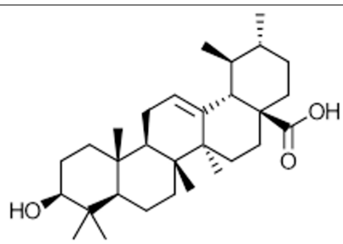
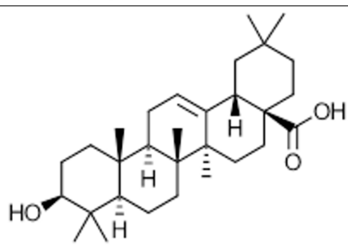
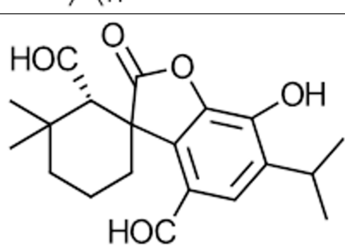
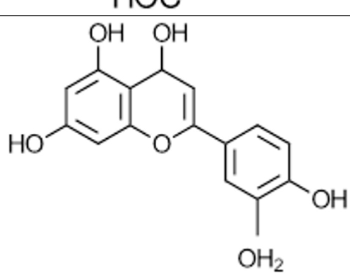


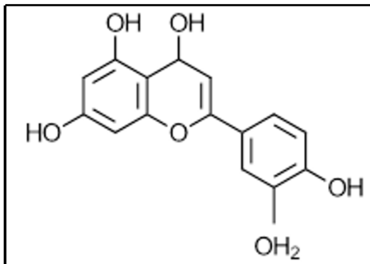
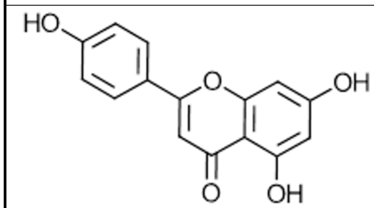
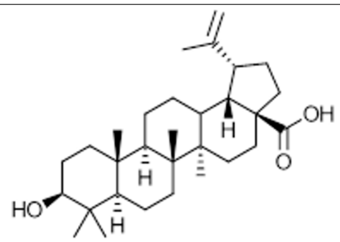
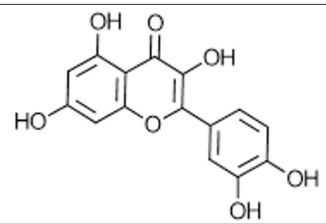
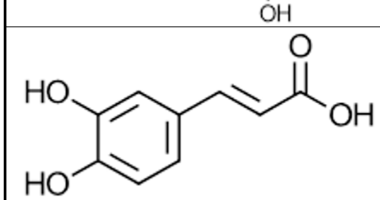
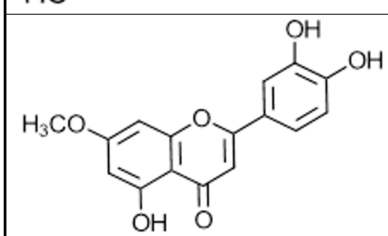
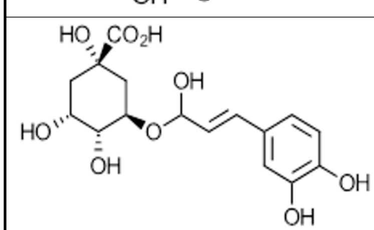
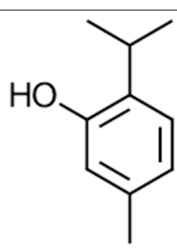
FIGURE 3. Main types of secondary metabolites in plants.

TABLE 1. **Secondary metabolites for *S. rosmarinus*.**

Structure	Compound	Biological Activity	Ref.
	1,8-cineole	Antimicrobial Activity, Proliferative and antioxidant activity	[22] [23] [24] [25]
	α-pinene	Antiproliferative Activity, Antimicrobial Activity, Antioxidant activity, Green pesticide and anticarcinogenic Activity	[26] [27] [23] [28] [29] [24]
	Camphene	Fumigant activity, Anticarcinogenic activity	[30] [31]
	β-pinene	Antioxidant activity, Photoprotective activity, Insecticidal and repellent activity	[24] [29] [32]
	Camphor	Anticancer Activity, Antimicrobial Activity, Antimicrobial Activity, Antimicrobial Activity, Antioxidant activity, Food preservative	[33] [34]
	Borneo	Anticancer Activity, Antioxidant Activity, Anti-inflammatory Activity, Analgesic Activity	[35] [2]
	Bornyl acetate	Immunomodulatory Activity, Anti-inflammatory Activity, Sedative Activity	[36]
	β-caryophyllene	Anticoccidial Activity, pesticide, Proliferative Activity, Activity against cardiac hypertrophy	[37] [38] [25]

	P-cymene	Antioxidant activity, Anti-inflammatory Activity, Antiparathyroid Activity, Antiproliferative Activity and Antidiabetic Activity.	[39]
	β-myrcene	Chemoprophylactic Activity	[40]
	Limonene	Antiproliferative Activity, Photoprotective Activity, Anticancer activity, Anticancer activity, Antioxidant activity	[41] [32]
	γ -terpinene	Antioxidant activity, Photoprotective Activity	[42] [32]
	Geraniol	Bactericidal Activity, Antimicrobial Activity, Antimicrobial Activity, Fungicidal Activity, Anti-inflammatory Activity	[43]
	Carnosol	Anticarcinogenic, antimicrobial, antiinflammatory	[44] [45]
	Rosmarinic Acid	Antioxidant, anti-inflammatory, anti-microbial	[46] [47] [48]
	Rosmaridiphenol	Anti-tumor, anti-inflammatory, neuroprotective	[49]

	Carnosic acid	Antioxidant, anti-inflammatory, anti-microbial	[46] [47] [48] [50]
	Isorosmanol	Antimicrobial, anti-inflammatory, anticarcinogenic	[51]
	Elenolic acid	Antioxidant, anti-inflammatory, anti-microbial	[52]
	Rosmanol	Anticarcinogenic, antimicrobial, antiinflammatory	[53]
	Ursolic acid	Antioxidant, anti-inflammatory, anticarcinogenic	[54]
	Oleanolic acid	Anti-tumor, anti-inflammatory, neuroprotective	[55]
	Rosmadial	Antioxidant, anti-inflammatory, anti-microbial	[56] [57] [48]
	Luteolin	Antioxidant, anti-inflammatory, anticarcinogenic	[56]

	Luteolin	Antioxidant, anti-inflammatory, anticarcinogenic	[56]
	Apigenin	Anticarcinogenic, antimicrobial, antiinflammatory	[56]
	Betulinic acid	Anti-tumor, anti-inflammatory, neuroprotective	[58] [59]
	Quercetin	Anticarcinogenic, antimicrobial, antiinflammatory	[60] [61]
	Caffeic acid	Anticarcinogenic, antimicrobial, antiinflammatory	[46] [57]
	Genkwanin	Antioxidant, anti-inflammatory, anticarcinogenic	[56]
	Colorogenic acid	Anticarcinogenic, antimicrobial, anti-inflammatory,	[62] [63]
	Thymol	Antioxidant, antimicrobial, anti-inflammatory, anticarcinogenic	[64]

Anticarcinogenic activity

The constitution of the human diet is one of the most substantial factors influencing the risk of developing cancer; the components of the diet can contribute either positively or negatively to the likelihood of contracting such a condition. Chemoprevention is the long-term pharmacological control of the risk of cancer, for which a myriad of plants and their components have been analyzed for their potential anticarcinogenic Activity. Around 60 % of the drugs used today in cancer treatment are derived from natural products[65][66].

As is well known, the *S. rosmarinus* plant exhibits significant antioxidant activity, inhibiting genotoxicity and providing protection against carcinogens or toxic agents. However, the side effects of therapeutic methods largely hinder their effectiveness, increasing the demand for new research on more efficient methods and treatments in the fight against cancer[67].

Polyphenols are chemical compounds capable of inducing cell differentiation and modulating growth, causing interference in tumor development and progression. Since *S. rosmarinus* is rich in various phenolic compounds, numerous studies focus on the anticarcinogenic Activity that this plant may exhibit. Some diterpenic polyphenols, such as carnosol and carnosic acid, are chemical compounds present in the dried leaves of *S. rosmarinus* at a 5 % concentration. It is reported that these compounds are largely responsible for the anticarcinogenic Activity[25][68].

Antioxidant capacity

Natural plant-derived antioxidants are becoming increasingly important, not only around food preservation and stability but also in preventive medicine. The Lamiaceae family has been highly relevant in research on antioxidant compounds, thanks to the high concentration of polyphenols. Antioxidants play a crucial role in the prevention and treatment of diseases associated with oxidative damage, such as cancer, cardiovascular diseases, and neurodegenerative diseases. Free radicals, reactive oxygen species, and hydrogen peroxide are inevitably produced by living organisms in metabolic processes. Continuous exposure to free radicals causes functional and structural damage, such as aging and cell death[69].

The antioxidant capacity of *S. rosmarinus* is due to the phenolic compounds present in the plant, which can inhibit the production of reactive species. The accumulation of these species has a negative effect on various organs and even systems of the human body[70]. Various studies have demonstrated that this property is directly related to the concentration of phenolic diterpenes. However, the content of these antioxidant molecules depends on different factors, including seasonal variations, environmental influences, species, origin, and plant growth. As mentioned earlier, antioxidants are chemical compounds that can inhibit and delay the oxidation of different lipids and biomolecules. They prevent the initiation of a chain reaction by radicals or propagation, which can cause functional damage in the human body, such as cancer or cardiovascular diseases. An antioxidant can prevent such processes due to its redox properties, such as hydrogen donation, reducing behavior, or quenching of singlet molecular oxygen[71][72].

In 2008, Wang *et al.*, examined the in vitro antioxidant activity of the essential oil of *S. rosmarinus* obtained through steam distillation, compared to three of its main components (α-pinene, 1,8-cineole, β-pinene). The oil and components were subjected to evaluation of their antioxidant activity using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, with ascorbic acid used as a positive control. The inhibition percentages of the radical were 62.45 %, 42.7 %, 45.61 %, and 46.21 % for the essential oil of *S. rosmarinus*, α-pinene, 1,8-cineole, and β-pinene, respectively. In general, the essential oil showed higher antioxidant activity than its components[73].

In 2015, Chen *et al.*, used the ABTS (2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid)) and FRAP (ferric ion reduction) techniques to assess the antioxidant activity of aqueous extracts of *S. rosmarinus*[72]. In 2023, Perales and collaborators demonstrated the antioxidant capacity of *S. rosmarinus* using the DPPH technique. The plant was collected from Iturbide, Nuevo León. They obtained the extracts through ultrasound-assisted maceration at 40 KHz for 60 minutes at room temperature, with a ratio of 1:12.5, solid: liquid. Antioxidant capacity was measured at 519 nm using a spectrophotometer, and ascorbic acid was used as a positive control. Subsequently, serial dilutions were performed, and the extracts were evaluated in triplicate. The authors successfully demonstrated an antioxidant capacity of 31.653 (IC50(μg/mL)), even higher than that of the ascorbic acid control[68].

Antioxidant capacity

Most plants produce secondary metabolites with antimicrobial Activity in response to the attack of pathogens or their normal course of growth and development. The increasing use of essential oils or aqueous extracts represents a new way to combat the proliferation of microorganisms. The escalating use of antibiotics in medicine, agriculture, and livestock has contributed to the growing resistance of various microorganisms to drugs. Drug resistance has been categorized as a global health problem, prompting an increasing number of researchers to delve into the investigation of new bioactive antimicrobial compounds. Several studies have examined the antimicrobial capacity of the *S. rosmarinus* plant against a broad spectrum of gram-positive bacteria (*S. aureus, S. pyogenes, S. pneumoniae*) and gram-negative bacteria (*E. coli, S. typhi*)[74][75].

Its antimicrobial Activity is primarily attributed to carnosol, carnosic acid, and rosmarinic acid. *S. rosmarinus* extracts have bioactive properties and antimicrobial Activity, stimulating anticarcinogenic Activity and phagocytosis by inactivating adhesins, enzymes, and transport proteins in bacteria. Flavonoids tend to form soluble protein complexes in the bacterial wall, which destroy it in response to microbial infection. On the other hand, essential oils exhibit antiseptic and antimicrobial capabilities attributed to bioactive compounds present in this plant, such as camphor, α-pinene, 1,8-cineole, eucalyptol, verbenone, limonene, borneol, and camphene. The mechanism of action of diterpenes involves lysing the bacterial cell membrane due to their lipophilic compounds, including some triterpene alcohols like alpha and beta-amyrin, as well as acids such as oleanolic acid and ursolic acid[76].

The *S. rosmarinus* extract acts at the cellular membrane level, increasing permeability and causing distortion of the cell wall in both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. The following are descriptions of some in vitro studies demonstrating the antimicrobial capacity of the *S. rosmarinus* plant. In 2010, Castaño *et al.*, demonstrated the antimicrobial activity of the essential oil and ethanolic extract of *S. rosmarinus*, obtained through steam distillation and maceration, respectively, against Gram-positive and Gram-negative bacteria, including *S. aureus, E. coli, S. sonnei, S. typhimurium, P. aeruginosa,* and *L. monocytogenes*, using the minimum inhibitory concentration (MIC) technique through microdilution colorimetry in broth. For the ethanolic extract, they subjected dried *S. rosmarinus* leaves to 95 % ethanol for 48 hours, followed by preconcentration using a rotary evaporator and finally lyophilization. Meanwhile, for the oil, dehydrated leaves were used, and the oil was obtained by steam distillation. The inoculum was obtained from an exponentially growing culture, and an aliquot of the inoculum was adjusted to 0.5 McFarland (1.5 x 108 CFU/mL). The essential oil exhibited antimicrobial Activity against a wide variety of Gram-positive and Gram-negative bacteria. The growth inhibition of Escherichia coli was achieved at a concentration of 4096 ppm, while for *Shigella sonnei* and *Staphylococcus aureus*, it was at 512 ppm. On the other hand, in the ethanolic extract, concentrations of 1024 ppm were obtained for S. *sonnei, S. typhimurium,* and *L. monocytogenes*. Greater sensitivity was observed in Gram-negative bacteria compared to Gram-positive ones, and the compound with the broadest inhibition spectrum was the essential oil, attributed to increased permeability and changes in the structure of the cell membrane[77].

Solano and Zambrano, in 2016, demonstrated the inhibition of the oil and aqueous phase extracts of *S. rosmarinus* against *S. mutans*. They used dried leaves of *S. rosmarinus*, which were macerated with distilled water for three days with continuous agitation at room temperature. Subsequently, the extract was filtered, and the water was evaporated for 18 hours at 70 °C. On the other hand, the oily extract was obtained through steam distillation. To establish the concentration of the extracts, the broth dilution method was performed to obtain the minimum bactericidal concentration (MBC). They observed that the aqueous extracts showed no inhibition against *Streptococcus mutans*, while the oily extracts exhibited inhibitions of 11.93 mm[78].

Montero *et al*., in 2017, demonstrated the antimicrobial Activity of the oily extract of the *S. rosmarinus* plant against *E. coli*, obtaining inhibition zones of 10.90 mm at a concentration of 80 %[79].

On the other hand, Karadag *et al*., in 2019, for the antimicrobial tests, ground *S. rosmarinus* leaves with methanol for 24 hours, filtered and evaporated, to obtain subfractions. These subfractions were prepared using liquid-liquid extraction with hexane and ethyl acetate, respectively. These authors demonstrated that the hexane fractions are susceptible to *S. aureus*, obtaining a minimum bactericidal concentration of 500 µg/mL[2].

Pharmacological and therapeutic studies

Medications and plant-based treatments for the management of various diseases are complementary approaches in medicine due to their few side effects[80]. Filiptsova *et al.*, in 2018, conducted a study to observe the effects of lavender and *S. rosmarinus* essential oils, obtained through steam distillation, on short-term human memory. They obtained the oils using steam distillation. The study involved 79 high school students (34 boys and 45 girls) aged 13 to 17 years, residing in the Ukrainian metropolis. Participants were divided into 3 groups: the control group (not exposed to any oil), the group sprayed with lavender oil, and the *S. rosmarinus* group. A standard Petri dish was placed in each corner of the room, filled from the bottom with tap water at room temperature in a volume of 15 mL, and 10 drops of each essential oil were added. Statistically significant differences were found in the short-term memory productivity of participants in different groups. Therefore, *S. rosmarinus* and lavender essential oils significantly increased image memory compared to the control group. Inhalation of *S. rosmarinus* essential oil increased the memorization of numbers, while inhalation of lavender oil weakened the process[81].

El-Desouky *et al.*, in 2019, demonstrated the nephroprotective effect of green tea extract (GTE), rosmarinic acid (RA), and *S. rosmarinus* (RE) on acute renal toxicity initiated by N-nitrosodiethylamine (DEN) and promoted by ferric nitrilotriacetate (Fe-NTA) in Wistar rats. *S. rosmarinus* extract countered the initiation of diethylnitrosamine and ferric nitriloacetate-induced nephrotoxicity in rats. Rats were classified into 5 groups: Group 1 included healthy rats, Group 2 received DEN+Fe-NTA, Group 3 received 200 mg/kg body weight of RE-DEN-Fe-NTA, Group 4 received 1 g/kg of GTE-DEN-Fe-NTA, and Group 5 received 50 mg/kg of RA+DEN+Fe-NTA. RE, GTE and RA were administered orally for 14 days before a single intraperitoneal administration of DEN (160 mg/kg) until the end of the experiment. Eighteen days after DEN, a single intraperitoneal dose of Fe-NTA (5 mg Fe/kg) was administered to promote nephrotoxicity in rats. The kidneys of each group were histopathologically examined at intervals. GTE, RA, and RE exerted a protective effect against renal toxicity, with GTE showing a more pronounced effect on renal function parameters, while RA showed the best protective results[82].

Jaglanian and Tsiani, in 2020, demonstrated the inhibition of proliferation and survival of prostate cancer cells by acting on Akt (protein kinase B) and mTOR (protein). They used a methanolic extract of *S. rosmarinus* obtained using an ultrasonic probe. They found a significant inhibition of survival and proliferation of androgen-sensitive PC-3 prostate cancer cells, while normal prostatic epithelial cells PNT1A were not affected. Furthermore, treatment with *S. rosmarinus* induced apoptosis and reduced the migration of PC-3 prostate cancer cells[8].

Makaremi *et al.*, in 2021, inhibited tumor growth in mice with colorectal cancer CT-26 using alcoholic extracts of *S. rosmarinus* obtained through ultrasound-assisted extraction. These authors conducted the measurement of cell cytotoxicity through the MTT colorimetric assay, showing a concentration-dependent increase in cytotoxicity in the CT-26 cell group. Cell treatment with half the inhibitory concentration (IC50) of *S. rosmarinus*, turmeric, and the combination induced apoptosis. In vivo studies revealed that the combined treatment (*S. rosmarinus* with turmeric) inhibited tumor growth in mice transplanted with CT-26 cells without side effects, such as weight loss or renal and hepatic functional changes. Additionally, mice treated with the plant mixture exhibited a significant increase in the proportion of cytotoxic T lymphocytes. In conclusion, the results showed that the combination of *S. rosmarinus* with turmeric has the potential to inhibit the growth of the CT-26 cancer cell line, reducing tumor growth in mice with colorectal cancer[83].

Cytotoxicity of *S. rosmarinus*

It has been reported that the main bioactive compounds contained in the plant, such as rosmarinic acid (RA), chlorogenic, caffeic, and ρ-coumaric acids, carnosic acid (CA), oleanolic acid, betulinic acid, ursolic acid, rosmanol, and carnosol (CR), exhibit no toxicity. However, some individuals sensitive to the bioactive compounds in this plant may experience allergies or contact dermatitis. Similarly, the use of this plant is not recommended for individuals with conditions such as gallstones without prior consultation with a doctor. While intoxication from *S. rosmarinus* infusions is not common, an overdose could lead to consequences such as vomiting, hemorrhages, uterine gastroenteritis, renal irritation, and abdominal spasms. Regarding the essential oil of *S. rosmarinus*, in much higher concentrations, it can be toxic to the central nervous system and may induce seizures[5][84].

Extraction technologies

In recent years, a wide variety of methods have been used for obtaining bioactive compounds from different plants, such as conventional heating extraction, aqueous alkaline extraction, solid-liquid extraction, extraction with conventional or traditional solvents, extraction with vegetable oils, and extraction using emerging technologies such as microwave and ultrasound, among others. However, extraction methodologies that are more environmentally friendly and do not compromise bioactive compounds during the extraction process have been preferred[85]. To achieve this, a possible solution could involve the use of emerging techniques and the implementation of green solvents. Table 2 shows the advantages and disadvantages of conventional methods compared to ultrasound.

TABLE 2. **Advantages and disadvantages of conventional methods compared to ultrasound.**

Extraction	Advantages	Disadvantages
Soxhlet extraction	High extraction efficiencies, no filtration or centrifugation required.	Use of non-polar organic solvents, thermal degradation of bioactive compounds, solvent boiling temperatures.
Maceration	Variety of solvents, simplicity of operation.	Long extraction times (hours, weeks), requires filtration, high extraction temperatures.
Infusion	Extraction of soluble and volatile compounds, variety of temperatures, shorter extraction times compared to maceration.	Long extraction times (hours), concentration of the extract obtained and filtration.
Decoction	Implementation of hard samples (seeds and stems).	Limited to thermostable and water-soluble bioactive compounds, high temperatures (boiling).
Conventional heating	Extraction of oils and bioactive compounds, rapid extraction.	High temperatures, use of toxic solvents, high energy requirements and decomposition of thermally sensitive components.
Ultrasonic extraction	Use of safe solvents, room temperature, low energy requirement, high extraction efficiencies, short extraction times (minutes).	Liquid samples, solvent required, difficult extraction process for viscous samples.

The extraction of bioactive and phytochemical compounds from plants is relevant due to the range of applications in the therapeutic, pharmaceutical, and food industries. This leads to the search for more efficient techniques that aid in the extraction of purer compounds with higher extraction yields. Several factors have been reported to limit or favor extraction techniques, such as the source or raw material, temperature, and solvent used. The current interest is in developing efficient and environmentally friendly techniques. Therefore, there is a notable focus on green or emerging techniques, including ultrasound-assisted extractions, supercritical fluids, pressurized liquids, microwaves, and cold plasma. These techniques, whether used individually or in combination, offer significant advantages over conventional methods, such as reducing high concentrations of solvents, shorter extraction times, lower temperatures, and higher quantitative and qualitative yields[86][87]. As described by Chemat, "Green extraction is based on extraction methodologies and processes that reduce energy consumption, allow the use of alternative solvents, and produce renewable natural products, ensuring a safe and high-quality extract or product."[88], Ultrasound extraction addresses some of the limitations of conventional techniques and incorporates key points of "green extraction"[89].

Ultrasound

Richards and Loomis first studied the effects of ultrasound in 1927, successfully solubilizing dimethyl sulfate in an alkaline solution. The case was forgotten for about 60 years; however, around the 1980s, sonochemistry experienced a revival and was highly implemented in different areas. Most modern devices rely on transducers (converters of electrical or mechanical energy into sound energy) for the generation of ultrasonic energy, which are made up of piezoelectric materials. If ultrasound is applied to a system, chemical changes can occur due to the generation and implosion of cavitation bubbles[90][91].

The cavitation phenomenon was first identified and reported in 1895 by Thorneycroft and Barnaby. It is based on the formation of cavitation bubbles, which grow until they collapse due to the pressure formed by their surroundings, as shown in Figure 4. Cavitation bubbles generate local heating and high pressure, known as a hot spot[92].

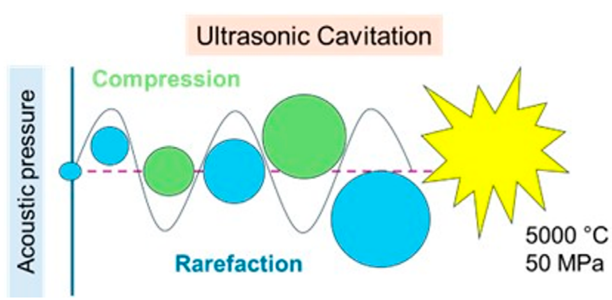


FIGURE 4. Process of ultrasonic cavitation.

Ultrasound is defined as sound of high frequency, which is above the limit at which the human ear can respond. The range of human hearing is generally considered to be between 16 Hz and 18 kHz, while ultrasound is typically considered to have frequencies between 20 kHz and 100 MHz. Sonochemistry usually operates in the range of around 20 to 40 kHz, although current sonochemical research explores broader ranges[93].

The ultrasound equipment was designed based on a piezoelectric transducer to treat solid materials in a liquid medium, such as ultrasound baths and ultrasound probes, as shown in Figure 5. Ultrasound baths have been widely used in industries for cleaning and extracting bioactive compounds, such as in the pharmaceutical, cosmetic, and ornamental industries. They consist of a transducer, a tank, a timer probe, and a heater. Indirect sonication is more effective as it is non-invasive, does not affect the degradation of bioactive compounds, and eliminates foam formation. On the other hand, direct sonication using an ultrasound probe is the most commonly used method, as it directly transfers ultrasound intensity to the sample, resulting in higher extraction efficiency and significantly reducing the time compared to the bath[94][95].

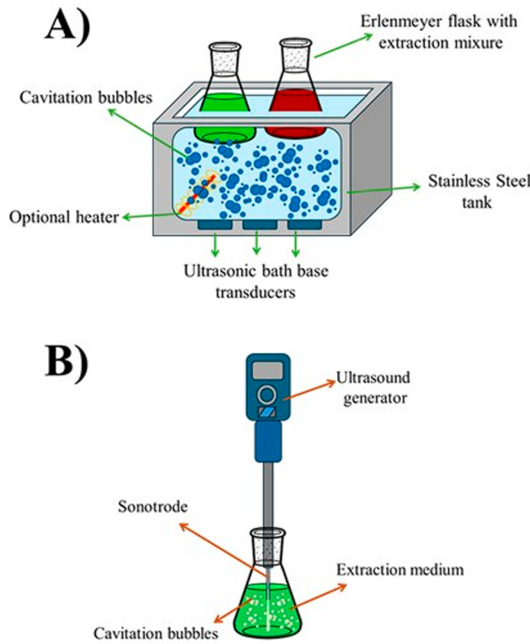


FIGURE 5. **Ultrasonic bath (A) and ultrasonic probe (B)**

Some of the most important factors to consider when implementing this technique for the extraction of bioactive compounds include considering the equipment's power, also expressed as the percentage of amplitude ranging from 0 to 100 %. This amplitude is linear to power. It has been reported that the power used for each selected plant sample depends entirely on the type of sample. However, working with powers in the range of 20 to 70 W and amplitudes of 30 to 80 %, the extraction yield increases with the increase in power and subsequently decreases after reaching a peak. This is explained by the increase in violent cavitation effects, which increases with the power. The size of the resonant bubble is directly proportional to the power, and as it increases, the size of the bubble and its implosion also intensify. This leads to greater sample fragmentation, pore formation, and higher extraction yields[96].

Other factors to consider include the equipment frequency, duty cycles, relaxation, extraction time, as well as the solvent-solid ratio and temperature. However, these factors show a trend where, as time, solvent-solid ratio, or frequency increases, the extraction percentages also increase until reaching a peak, after which they start to decrease. Therefore, optimal extraction design by varying these factors is important to obtain good extraction yields, which directly depend on the type of material used[97][98]. In addition to selecting the appropriate parameters for extraction, it is crucial to consider energy consumption. Ultrasound equipment requires electrical energy for operation. Taking this into account, it is essential to measure the energy consumption during extraction. Nowadays, some researchers use a wattmeter to calculate energy expenditure. These calculations are based on the assumption that 1 kWh of energy generates 800 g of CO_2 during the combustion of fossil fuels, which is released into the atmosphere[99].

The choice of the appropriate solvent for the extraction of bioactive compounds depends on physical properties such as surface tension, viscosity, and vapor pressure. These physical characteristics of solvents directly affect the cavitation phenomenon. Cavitation has been observed in solvents with high vapor pressure, low viscosity, and low surface tension. However, high cavitation intensity has also been observed in solvents with low vapor pressure, high viscosity, and high surface tension. Various solvents have been used for the extraction of bioactive compounds, with the most popular ones being methanol, ethanol, and different water ratios. Currently, there is an increasing focus on research into the implementation of deep eutectic solvents, particularly environmentally friendly ones[94]. Table 3 shows the main parameters governing the extraction of bioactive compounds.

The advantages derived from the use of extracts and the growing interest in research have led to the development of various technologies that can enable better extraction without compromising the final product. One emerging technology that has shown substantial advantages over traditional maceration, conventional heating, and Soxhlet extraction is the use of ultrasound-assisted extraction, which is characterized as a high-efficiency, low-cost, environmentally friendly extraction method with flexibility to integrate with other treatment processes[100].

TABLE 3. **Advantages and disadvantages of conventional methods compared to ultrasound.**

Plant Matter	Bioactive Compounds	Ultrasonic Parameters	Solvent Used	Ref.
Tradescantia zebrina leaves	Phenolics and anthocyanins	6.25 min, 60 °C and 20 % amplitude.	Water	[102]
Papaya pulp and skin	Antioxidants	30 °C, 19.70-16.46 min.	Ethanol-water (60:30)	[103]
Hypnea flagelliformis	Antioxidants and phenolics	Power 80%, time 30 min.	choline chloride and lactic acid (1:2) with 20 % water	[104]
Fresh *Eucalyptus globulus* leaves	Terpenes and phenolic compounds	Terpenes: pH 4, 80 W, 40 °C, 15 min. Polyphenols: pH 4, 120 W, 50 °C, 15 min.	Ethanol-water (60:30)	[105]
Byrsonima crassifolia	Antioxidant compounds	0.04 W/cm^3, 105 min, 50 °C.	Ethanol-water (70:30)	[106]
Solanum torvum Sw	Polyphenols y flavonoids	50–60 W cm^{-2}, 30-45 °C.	Methanol-water (55:65)	[107]
Rubus idaeus L.	Anthocyanins and phenolic compounds	60 min.	Eutectic solvent -water (1:1) (Acetic acid, formic acid, lactic acid, maltose, and glucose)	[108]

Extraction of bioactive compounds using ultrasound

Ultrasound-assisted extraction is carried out by creating cavitation bubbles that generate thermal and mechanical points within plant cells, as show in Figure 6. This leads to the rupture of the cell wall and the release of bioactive compounds into a solvent through diffusion. The extraction mechanism involves unique and combined mechanisms such as cellular alteration and mass transfer. It has been reported that the cavitation phenomenon creates pores, microchannels, and cavities in plant material, facilitating the penetration of solvent molecules and promoting extraction. Additionally, studies indicate that wet plant material is more effective. On the other hand, research suggests that 20 kHz ultrasound can break hydrogen bond and glycosidic linkages, change amide functional groups to carboxyls, and enhance extraction[101].

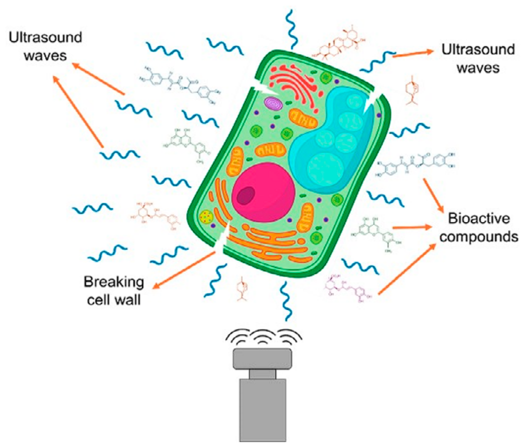


FIGURE 6. Breaking cell wall by ultrasound waves.

Albu *et al.*, in 2004, reported the use of ultrasound to improve the extraction processes of carnosic acid from *S. rosmarinus* using butanone, ethyl acetate, and ethanol as solvents, both from dry and fresh leaves. They found that sonication improved the yields of carnosic acid for all three solvents and shortened the extraction times. They also mentioned that sonication improved the choice of less aggressive solvents, such as ethanol, because ethanol is a poor solvent under conventional conditions (high pressures and temperatures) and achieved a similar extraction efficiency compared to the other two solvents used. Extraction from dry herb with ethanol proved to be more efficient than that from fresh material, which they attributed to the water present in fresh leaves[109].

On the other hand, Paniwnyk *et al.*, in 2009, studied the effect of ultrasound on the extraction of antioxidants from *S. rosmarinus* using solvents compared to conventional heating. They found that ultrasound provides more efficient extraction by increasing the extraction by 66 % of rosmarinic acid (mg/g) at temperatures of 35 °C and with less dependence on the extraction solvent used compared to the conventional heating method. They also reported that the application of this technique is possible for the extraction of bioactive compounds with antioxidant activity[110].

In 2016, a study was conducted on the antioxidant activity and rosmarinic acid content in ethanolic extracts of six medicinal plants (*L. angustifolia, H. perforatum, S. officinalis, M. sylvestris, M. officinalis, S. rosmarinus*) using ultrasound technique with a frequency of 35 kHz for 15 minutes. The study reported that all plants showed antioxidant activity greater than 70 % (0.1 g/ml), except for L. angustifolia and M. sylvestris. They also reported that all plants contain rosmarinic acid. In conclusion, they found that ultrasound is a fast and effective technique for preserving antioxidant activity and rosmarinic acid content in a matter of minutes[111].

Zhong *et al.*, in 2021, reported the extraction of polar extracts from *S. rosmarinus* using ethanol. They found two new compounds and six already known compounds, with most of the isolated compounds showing significant antimicrobial properties, with minimum concentration values ranging from 2 to 128 μg/mL. However, these inhibitions were weaker than those obtained with the polar fraction. Additionally, the polar fraction was reported as a promising food additive due to its higher antimicrobial activity than the essential oil[112]. Table 4 shows some references of extraction of bioactive compounds from *S. rosmarinus*. using ultrasound as an extraction method.

TABLE 4. **Advantages and disadvantages of conventional methods compared to ultrasound.**

Plant Matter	Bioactive Compounds	Extraction efficiency	Results	Ref.
S. rosmarinus	Carnosic acid and rosmarinic acid	24.0 ± 0.3 mg$_{CA}$*g^{-1}$_{Biomass}$ 8.4 ± 0.3 mg$_{RA}$*g^{-1}$_{Biomass}$	Ultrasonic extraction is more effective in only 10 min compared to 48 h of agitation.	[113]
S. rosmarinus	Rosmarinic acid	Extraction yield 6.10 %	The best extraction yield was obtained with a natural deep eutectic solvent.	[114]
S. rosmarinus	Rosmarinic acid and carnosol	C: 5.61 ± 1.96 mg/g RA: 3.61 ± 0.94 mg/g	A yield increase of 11 % was obtained with eutectic solvents compared to organic solvents.	[115]
S. rosmarinus	Rosmarinic acid and carnosol	Extraction yield 13.73 % and C+CA 17.63 mg/100g	High C+CA concentrations were obtained with short extraction times (10 min) and relatively low temperatures (30 °C).	[116]
M. officinalis	Rosmarinic acid	86.3 ± 4.1 mgRA/gplantaseca	The ultrasound technique proved to be more efficient than microwave and conventional heating, in addition to reducing the extraction temperature and time.	[117]
S. rosmarinus	Ursolic acid and carnosic acid	Extraction yield 18.8 ± 2.2 % CA: 15.4 ± 0.0 mg/grosmary UA: 35.3 ± 0.0 mg/grosmary	The ultrasound technique proves to be more efficient than Conventional Solvent Extraction, Controlled Instant Pressure Drop Deodorization, Pressurized Liquid Extraction, Microwaves, Subcritical Extraction with Water, Supercritical Fluid Extraction, and Ionic Liquids. Additionally, it is the technique with the lowest carbon emissions and the lowest energy consumption.	[118]
S. rosmarinus	Flavonoids and rosmarinic acid	Extraction yield 22 % F:10.3 mg/g RA: 4.8 mg/g	The ultrasound technique proved to be the most suitable for the extraction of bioactive compounds compared to the microwave technique and conventional methods.	[119]
P. scutellarioides	Rosmarinic Acid	118 mg/g	The best extraction conditions were obtained using ultrasound for a duration of 45 minutes and a frequency of 30 kHz.	[120]
S. rosmarinus	Carnosic acid and rosmarinic acid	Extraction yield 100 %	It was demonstrated that the proposed approach has higher efficiency, a shorter extraction time, and is a new alternative for the extraction of carnosic acid and rosmarinic acid compared to traditional reference methods, in addition to the use of ionic liquids.	[121]
S. officinalis	Carnosic acid and carnosol	CA:147.5 mg/100g C:42.7 mg/100g	They report ultrasound-assisted extraction as a green, simple, and safe technique for extracting bioactive compounds. They also report higher concentrations of analytes compared to the maceration technique.	[122]
S. rosmarinus	Carnosic and rosmarinic acids	CA: 62.19 ± 0.903 RA: 54.14 ± 0.786	The ultrasound technique shows great potential as an ecological method to obtain *S. rosmarinus*. extract rich in antioxidants with higher concentrations of polyphenolic constituents compared to the supercritical extraction method.	[123]

*** CA: Carnosic acid, RA: Rosmarinic acid, C: Carnosol, F: Flavnoides, UA: Ursolic acid.**

CONCLUSIONS

The *S. rosmarinus* plant has been used since ancient times, from home remedies to therapeutic applications. Currently, it has gained significant importance in various fields of research due to its culinary, antioxidant, antimicrobial, and therapeutic properties resulting from its secondary metabolites, such as rosmarinic acid, carnosol, and carnosic acid, among others. Although conventional methodologies used for extracting bioactive compounds from *S. rosmarinus* are widely employed today, there is still a search for more environmentally sustainable methods that allow a reduction in solvents, high temperatures, and waste generation.

The use of non-conventional technologies such as ultrasound has successfully improved extraction percentages and the selectivity of *S. rosmarinus* components compared to thermal and hydrothermal methods, with enhanced extraction yields when using poor solvents like ethanol, which is a less effective solvent in conventional extractions. Furthermore, emerging technologies enable the industrial scaling of extraction and open new possibilities for implementing various metabolites from natural resources in a wide range of applications, from culinary to therapeutic areas.

ACKNOWLEDGEMENTS

We would like to thank the Faculty of Chemical Sciences for providing the necessary facilities to carry out the Postgraduate Studies in Science and Technology of Materials, CONAHCYT for the granted scholarships 863187 and 771323, as well as the support provided by CONAHCYT through the SEP-CONACyT Basic Sciences Project 2017-2018 CB2017-2018 A1-S-44977.

DECLARATION OF CONFLICT OF INTEREST

All authors declare that there is no personal or financial relationship with other individuals or organizations that could inappropriately influence or bias the work.

CONTRIBUTIONS OF THE AUTHORS

J. J. C. P. conceptualized the project, wrote, reviewed and edited the different versions of the manuscript, carried out analysis, designed and developed the methodology. W. Y. V. L. participated in the investigation, carried out analyses, wrote, reviewed and edited different versions of the manuscript. A. O. C. F. carried out analysis and oversaw the project. S. C. E. G. carried out analyses and reviewed and edited different versions of the manuscript. E. M. M. R. carried out analyses and reviewed and edited the manuscript. A. S. G. conceptualized the project, designed and developed the methodology, wrote, reviewed and edited the different versions of the manuscript, funding acquisition, wrote, reviewed and edited the different versions of the manuscript. All authors reviewed and approved the final version of the manuscript.

REFERENCES

[1] I. Messaoudi Moussii, K. Nayme, M. Timinouni, J. Jamaleddine, H. Filali, and F. Hakkou, "Synergistic antibacterial effects of Moroccan Artemisia herba alba, Lavandula angustifolia and Rosmarinus officinalis essential oils," Synergy, vol. 10, art. no. 100057, Jun. 2020, doi: https://doi.org/10.1016/j.synres.2019.100057

[2] A. E. Karadağ, B. Demirci, A. Çaşkurlu, F. Demirci, M. E. Okur, D. Orak, H. Sipahi, K. H. C. Başer, "In vitro antibacterial, antioxidant, anti-inflammatory and analgesic evaluation of Rosmarinus officinalis L. flower extract fractions," South Afr. J. Bot., vol. 125, pp. 214-220, Sep. 2019, doi: https://doi.org/10.1016/j.sajb.2019.07.039

[3] A. Manilal, K. R. Sabu, M. Shewangizaw, A. Aklilu, M. Seid, B. Merdikios, B. Tsegaye, "In vitro antibacterial activity of medicinal plants against biofilm-forming methicillin-resistant Staphylococcus aureus: efficacy of Moringa stenopetala and Rosmarinus officinalis extracts," Heliyon, vol. 6, no. 1, art. no. e03303, Jan. 2020, doi: https://doi.org/10.1016/j.heliyon.2020.e03303

[4] L. M. de Macedo, É. M. D. Santos, L. Militão, L. L. Tundisi, J. A. Ataide, E. B. Souto, P. G. Mazzola, "Rosemary (Rosmarinus officinalis L., syn Salvia rosmarinus Spenn.) and Its Topical Applications: A Review," Plants, vol. 9, no. 5, art. no. 651, May 2020, doi: https://doi.org/10.3390/plants9050651

[5] M. T. López Luengo, "El romero. Planta aromática con efectos antioxidantes," Offarm, vol. 27, no. 7, pp. 60-63, Jul. 2008. [Online]. Available: https://www.elsevier.es/es-revista-offarm-4-articulo-el-romero-planta-aromatica-con-13124840

[6] D. R. Berdahl y J. McKeague, "Rosemary and sage extracts as antioxidants for food preservation," in Handbook of Antioxidants for Food Preservation, F. Shahidi, Ed., Sawstin, United Kingdom: Elsevier, 2015, pp. 177-217, doi: https://doi.org/10.1016/B978-1-78242-089-7.00008-7

[7] J. L. Machado, A. K. Martins Assunção, M. C. Pinto da Silva, A. Silva Dos Reis, et al., "Brazilian Green Propolis: Anti-Inflammatory Property by an Immunomodulatory Activity," Evid. Based Complement. Alternat. Med., vol. 2012, art. no. 157652, 2012, doi: https://doi.org/10.1155/2012/157652

[8] A. Jaglanian and E. Tsiani, "Rosemary Extract Inhibits Proliferation, Survival, Akt, and mTOR Signaling in Triple-Negative Breast Cancer Cells," Int. J. Mol. Sci., vol. 21, no. 3, art. no. 810, Jan. 2020, doi: https://doi.org/10.3390/ijms21030810

[9] A. Ali, B. L. Chua, and Y. H. Chow, "An insight into the extraction and fractionation technologies of the essential oils and bioactive compounds in Rosmarinus officinalis L.: Past, present and future," TrAC - Trends Anal. Chem., vol. 118, pp. 338-351, Sep. 2019, doi: https://doi.org/10.1016/j.trac.2019.05.040

[10] R. S. Borges, B. L. S. Ortiz, A. C. M. Pereira, H. Keita, and J. C. T. Carvalho, "Rosmarinus officinalis essential oil: A review of its phytochemistry, anti-inflammatory activity, and mechanisms of action involved," J. Ethnopharmacol., vol. 229, pp. 29-45, Jan. 2019, doi: https://doi.org/10.1016/j.jep.2018.09.038

[11] Integrated Taxonomic Information System - Report , "Rosmarinus officinalis." ITIS. https://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN&search_value=32677&print_version=PRT&source=to_print#null (accessed Nov. 22, 2023).

[12] Anjali, S. Kumar, T. Korra, R. Thakur, et al., "Role of plant secondary metabolites in defence and transcriptional regulation in response to biotic stress," Plant Stress, vol. 8, art. no. 100154, Jun. 2023, doi: https://doi.org/10.1016/j.stress.2023.100154

[13] M. Lingwan, A. A. Pradhan, A. K. Kushwaha, M. A. Dar, L. Bhagavatula, and S. Datta, "Photoprotective role of plant secondary metabolites: Biosynthesis, photoregulation, and prospects of metabolic engineering for enhanced protection under excessive light," Environ. Exp. Bot., vol. 209, art. no. 105300, May 2023, doi: https://doi.org/10.1016/j.envexpbot.2023.105300

[14] M. F. Lemos, M. F. Lemos, H. P. Pacheco, D. C. Endringer, and R. Scherer, "Seasonality modifies rosemary's composition and biological activity," Ind. Crops Prod., vol. 70, pp. 41-47, Aug. 2015, doi: https://doi.org/10.1016/j.indcrop.2015.02.062

[15] D. Sadeh, N. Nitzan, D. Chaimovitsh, A. Shachter, M. Ghanim, and N. Dudai, "Interactive effects of genotype, seasonality and extraction method on chemical compositions and yield of essential oil from rosemary (Rosmarinus officinalis L.)," Ind. Crops Prod., vol. 138, art. no. 111419, Oct. 2019, doi: https://doi.org/10.1016/j.indcrop.2019.05.068

[16] C. Tschiggerl, F. Bucar, "Investigation of the Volatile Fraction of Rosemary Infusion Extracts," Sci. Pharm., vol. 78, no. 3, pp. 483-492, 2010, doi: https://doi.org/10.3797/scipharm.1004-23

[17] A.-H. Lo, Y.-C. Liang, S.-Y. Lin-Shiau, C.-T. Ho, and J.-K. Lin, "Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxide synthase through down-regulating nuclear factor-κB in mouse macrophages," Carcinogenesis, vol. 23, no. 6, pp. 983-991, Jun. 2002, doi: https://doi.org/10.1093/carcin/23.6.983

[18] F. A. Khalafalla, F. H. M. Ali, and A.-R. H. A. Hassan, "Quality improvement and shelf-life extension of refrigerated Nile tilapia (Oreochromis niloticus) fillets using natural herbs," Beni-Suef Univ. J. Basic Appl. Sci., vol. 4, no. 1, pp. 33-40, Mar. 2015, doi: https://doi.org/10.1016/j.bjbas.2015.02.005

[19] A. R. Gouveia, M. Alves, J. A. Silva, y C. Saraiva, "The Antimicrobial Effect of Rosemary and Thyme Essential Oils Against Listeria Monocytogenes in Sous Vide Cook-chill Beef During Storage," Procedia Food Sci., vol. 7, pp. 173-176, 2016, doi: https://doi.org/10.1016/j.profoo.2016.10.001

[20] M. Radaelli, B. P. da Silva, L. Weidlich, L. Hoehne, A. Flach, L. A. Mendonça Alves da Costa, E. M. Ethur, "Antimicrobial activities of six essential oils commonly used as condiments in Brazil against Clostridium perfringens," Braz. J. Microbiol., vol. 47, no. 2, pp. 424-430, Apr. 2016, doi: https://doi.org/10.1016/j.bjm.2015.10.001

[21] S. Adhikary and N. Dasgupta, "Role of secondary metabolites in plant homeostasis during biotic stress," Biocatal. Agric. Biotechnol., vol. 50, art. no. 102712, Jul. 2023, doi: https://doi.org/10.1016/j.bcab.2023.102712

[22] N. M. Vazquez, S. Moreno, and E. M. Galván, "Exposure of multidrug-resistant Klebsiella pneumoniae biofilms to 1,8-cineole leads to bacterial cell death and biomass disruption," Biofilm, vol. 4, art. no. 100085, Dec. 2022, doi: https://doi.org/10.1016/j.bioflm.2022.100085

[23] I. Oualdi, F. Brahmi, O. Mokhtari, S. Abdellaoui, A. Tahani, and A. Oussaid, "Rosmarinus officinalis from Morocco, Italy and France: Insight into chemical compositions and biological properties," Mater. Today Proc., vol. 45, pp. 7706-7710, 2021, doi: https://doi.org/10.1016/j.matpr.2021.03.333

[24] W. Wang, N. Wu, Y. G. Zu, and Y. J. Fu, "Antioxidative activity of Rosmarinus officinalis L. essential oil compared to its main components," Food Chem., vol. 108, no. 3, pp. 1019-1022, Jun. 2008, doi: https://doi.org/10.1016/j.foodchem.2007.11.046

[25] C. Bai, Q. Ma, Q. Li, L. Yu, D. Zhen, M. Liu, C. Wei, "Combination of 1,8-cineole and beta-caryophyllene synergistically reverses cardiac hypertrophy in isoprenaline-induced mice and H9c2 cells," Bioorg. Chem., vol. 124, art. no. 105823, Jul. 2022, doi: https://doi.org/10.1016/j.bioorg.2022.105823

[26] A. Kumar, K. Dev, and A. Sourirajan, "Essential Oils of Rosmarinus officinalis L., Cymbopogon citratus (DC.) Stapf., and the phyto-compounds, delta-carene and alpha-pinene mediate cell cycle arrest at G2/M transition in budding yeast Saccharomyces cerevisiae," South Afr. J. Bot., vol. 141, pp. 296-305, Sep. 2021, doi: https://doi.org/10.1016/j.sajb.2021.05.008

[27] M. Ghavam, "GC-MS analysis and antimicrobial activities of a Rosmarinus officinalis L. essential oil from Kashan Region (Iran)," Biochem. Syst. Ecol., vol. 105, art. no. 104507, Dec. 2022, doi: https://doi.org/10.1016/j.bse.2022.104507

[28] M. M. Karimkhani, M. Nasrollahzadeh, M. Maham, A. Jamshidi, M. S. Kharazmi, D. Dehnad, S. M. Jafari, "Extraction and purification of α-pinene; a comprehensive review," Crit. Rev. Food Sci. Nutr., pp. 1-26, Nov. 2022, doi: https://doi.org/10.1080/10408398.2022.2140331

[29] N. Boukraa, S. Ladjel, W. Benlamoudi, M. B. Goudjil, M. Berrekbia, and A. Eddoud, "Insecticidal and repellent activities of Artemisia herba alba Asso, Juniperus phoenicea L and Rosmarinus officinalis L essential oils in synergized combinations against adults of Tribolium castaneum (Herbst) (Coleoptera: Tenebrionidae)," Biocatal. Agric. Biotechnol., vol. 45, art. no. 102513, Oct. 2022, doi: https://doi.org/10.1016/j.bcab.2022.102513

[30] M. Ben Abada, S. Haouel Hamdi, C. Masseoud, H. Jroud, E. Bousshih, and J. Mediouni Ben Jemâa, "Variations in chemotypes patterns of Tunisian Rosmarinus officinalis essential oils and applications for controlling the date moth Ectomyelois ceratoniae (Pyralidae)," South Afr. J. Bot., vol. 128, pp. 18-27, Jan. 2020, doi: https://doi.org/10.1016/j.sajb.2019.10.010

[31] P. Satyal, T. H. Jones, E. M. Lopez, R. L. McFeeters, et al., "Chemotypic Characterization and Biological Activity of Rosmarinus officinalis," Foods, vol. 6, no. 3, art. no. 20, Mar. 2017, doi: https://doi.org/10.3390/foods6030020

[32] H. Bitterling, P. Lorenz, W. Vetter, D. R. Kammerer, and F. C. Stintzing, "Photo-protective effects of selected furocoumarins on β-pinene, R-(+)-limonene and γ-terpinene upon UV-A irradiation," J. Photochem. Photobiol. Chem., vol. 424, art. no. 113623, Feb. 2022, doi: https://doi.org/10.1016/j.jphotochem.2021.113623

[33] A. M. Eid, N. Jaradat, L. Issa, A. Abu-Hasan et al., "Evaluation of anticancer, antimicrobial, and antioxidant activities of rosemary (Rosmarinus Officinalis) essential oil and its Nanoemulgel," Eur. J. Integr. Med., vol. 55, art. no. 102175, Oct. 2022, doi: https://doi.org/10.1016/j.eujim.2022.102175

[34] B. Amina, B. Soumeya, B. Salim, B. Mahieddine, et al., "Chemical profiling, antioxidant, enzyme inhibitory and in silico modeling of Rosmarinus officinalis L. and Artemisia herba alba Asso. essential oils from Algeria," South Afr. J. Bot., vol. 147, pp. 501-510, Jul. 2022, doi: https://doi.org/10.1016/j.sajb.2022.02.012

[35] M. Saied, K. Ali, and A. Mosayeb, "Rosemary (Rosmarinus officinalis L.) essential oil alleviates testis failure induced by Etoposide in male rats," Tissue Cell, vol. 81, art. no. 102016, Apr. 2023, doi: https://doi.org/10.1016/j.tice.2023.102016

[36] Z. Zhao, Y. Sun, and X. Ruan, "Bornyl acetate: A promising agent in phytomedicine for inflammation and immune modulation," Phytomedicine, vol. 114, art. no. 154781, Jun. 2023, doi: https://doi.org/10.1016/j.phymed.2023.154781

[37] R. Aitfella Lahlou, M. Bounechada, A. Mohammedi, L. R. Silva, and G. Alves, "Dietary use of Rosmarinus officinalis and Thymus vulgaris as anticoccidial alternatives in poultry," Anim. Feed Sci. Technol., vol. 273, art. no. 114826, Mar. 2021, doi: https://doi.org/10.1016/j.anifeedsci.2021.114826

[38] E. Mahajan, S. Singh, Diksha, S. Kaur, and S. K. Sohal, "The genotoxic, cytotoxic and growth regulatory effects of plant secondary metabolite β-caryophyllene on polyphagous pest Spodoptera litura (Fabricius) (Lepidoptera: Noctuidae)," Toxicon, vol. 219, art. no. 106930, Nov. 2022, doi: https://doi.org/10.1016/j.toxicon.2022.09.016

[39] A. Balahbib, N. El Omari, N. El Hachlafi, F. Lakhdar, "Health beneficial and pharmacological properties of p-cymene," Food Chem. Toxicol., vol. 153, art. no. 112259, Jul. 2021, doi: https://doi.org/10.1016/j.fct.2021.112259

[40] J. Fabbri, M. A. Maggiore, P. E. Pensel, C. M. Albani, G. M. Denegri, and M. C. Elissondo, "Could beta-myrcene be an alternative to albendazole for the treatment of experimental cystic echinococcosis?," Acta Trop., vol. 187, pp. 5-12, Nov. 2018, doi: https://doi.org/10.1016/j.actatropica.2018.07.013

[41] T. D. Alexandrino, T. D. M. Medeiros, A. L. T. G. Ruiz, D. C. Favaro, G. M. Pastore, and J. L. Bicas, "Structural properties and evaluation of the antiproliferative activity of limonene-1,2-diol obtained by the fungal biotransformation of R -(+)- and S -(−)-limonene," Chirality, vol. 34, no. 6, pp. 887-893, Jun. 2022, doi: https://doi.org/10.1002/chir.23439

[42] Y. Guo, A. Baschieri, R. Amorati, and L. Valgimigli, "Synergic antioxidant activity of γ-terpinene with phenols and polyphenols enabled by hydroperoxyl radicals," Food Chem., vol. 345, art. no. 128468, May 2021, doi: https://doi.org/10.1016/j.foodchem.2020.128468

[43] A. Mouahid, C. Dufour, and E. Badens, "Supercritical CO2 extraction from endemic Corsican plants; comparison of oil composition and extraction yield with hydrodistillation method," J. CO2 Util., vol. 20, pp. 263-273, Jul. 2017, doi: https://doi.org/10.1016/j.jcou.2017.06.003

[44] M. Mueller, S. Hobiger, and A. Jungbauer, "Anti-inflammatory activity of extracts from fruits, herbs and spices," Food Chem., vol. 122, no. 4, pp. 987-996, Oct. 2010, doi: https://doi.org/10.1016/j.foodchem.2010.03.041

[45] D. Poeckel, C. Greiner, M. Verhoff, O. Rau et al., "Carnosic acid and carnosol potently inhibit human 5-lipoxygenase and suppress pro-inflammatory responses of stimulated human polymorphonuclear leukocytes," Biochem. Pharmacol., vol. 76, no. 1, pp. 91-97, Jul. 2008, doi: https://doi.org/10.1016/j.bcp.2008.04.013

[46] S.-Y. Yang, C.-O. Hong, G. P. Lee, C.-T. Kim, and K.-W. Lee, "The hepatoprotection of caffeic acid and rosmarinic acid, major compounds of Perilla frutescens, against t-BHP-induced oxidative liver damage," Food Chem. Toxicol., vol. 55, pp. 92-99, May 2013, doi: https://doi.org/10.1016/j.fct.2012.12.042

[47] W. Yeddes, H. Majdi, H. Gadhoumi, T. G. Affes, S. N. Mohamed, W. A. Wannes, M. Saidani-Tounsi, "Optimizing Ethanol Extraction of Rosemary Leaves and Their Biological Evaluations," J. Explor. Res. Pharmacol., vol. 7, no. 2, pp. 85-94, Jun. 2022, doi: https://dx.doi.org/10.14218/JERP.2022.00002

[48] Y. Zhang, J. P. Smuts, E. Dodbiba, R. Rangarajan, J. C. Lang, and D. W. Armstrong, "Degradation Study of Carnosic Acid, Carnosol, Rosmarinic Acid, and Rosemary Extract (Rosmarinus officinalis L.) Assessed Using HPLC," J. Agric. Food Chem., vol. 60, no. 36, pp. 9305-9314, Sep. 2012, doi: https://doi.org/10.1021/jf302179c

[49] M. S. Afonso, A. M. de o Silva, E. B. Carvalho, D. P. Rivelli, et al., "Phenolic compounds from Rosemary (Rosmarinus officinalis L.) attenuate oxidative stress and reduce blood cholesterol concentrations in diet-induced hypercholesterolemic rats," Nutr. Metab., vol. 10, no. 1, art. no. 19, Feb. 2013, doi: https://doi.org/10.1186/1743-7075-10-19

[50] J. M. Andrade, C. Faustino, C. Garcia, D. Ladeiras, C. P. Reis, and P. Rijo, "Rosmarinus officinalis L.: an update review of its phytochemistry and biological activity," Future Sci. OA, vol. 4, no. 4, art. no. FSO283, Apr. 2018, doi: https://doi.org/10.4155/fsoa-2017-0124

[51] S.-Y. Park, "Neuroprotective and Neurotrophic Effects of Isorosmanol," Z. Naturforsch. C. J. Biosci., vol. 64, no. 5-6, pp. 395-398, Jun. 2009, doi: https://doi.org/10.1515/znc-2009-5-616

[52] Y. Wang, Y. Wu, A. Wang, A. Wang, et al., "An olive-derived elenolic acid stimulates hormone release from L-cells and exerts potent beneficial metabolic effects in obese diabetic mice," Front. Nutr., vol. 9, art. no. 1051452, Nov. 2022, doi: https://doi.org/10.3389/fnut.2022.1051452

[53] L. Li, Z. Pan, D. Ning, and Y. Fu, "Rosmanol and Carnosol Synergistically Alleviate Rheumatoid Arthritis through Inhibiting TLR4/NF-κB/MAPK Pathway," Molecules, vol. 27, no. 1, art. no. 78, Dic. 2021, doi: https://doi.org/10.3390/molecules27010078

[54] F. Farhadi, V. Baradaran Rahimi, N. Mohamadi, and V. R. Askari, "Effects of rosmarinic acid, carnosic acid, rosmanol, carnosol, and ursolic acid on the pathogenesis of respiratory diseases," Biofactors, Dic. 2022, doi: https://doi.org/10.1002/biof.1929

[55] H. Feng, Y. Hu, S. Zhou, and Y. Lu, "Farnesoid X receptor contributes to oleanolic acid-induced cholestatic liver injury in mice," J. Appl. Toxicol., vol. 42, no. 8, pp. 1323-1336, Aug. 2022, doi: https://doi.org/10.1002/jat.4298

[56] H. Kheiria, A. Mounir, Q. María, J. María José, and S. Bouzid, "Total Phenolic Content and Polyphenolic Profile of Tunisian Rosemary (Rosmarinus officinalis L.) Residues," in Natural Drugs from Plants, H. A. El-Shemy, Ed., IntechOpen, 2021, ch. 9, doi: https://doi.org/10.5772/intechopen.97762

[57] M. Romo Vaquero, M.-J. Yáñez-Gascón, R. García Villalba, M. Larrrosa, et al., "Inhibition of Gastric Lipase as a Mechanism for Body Weight and Plasma Lipids Reduction in Zucker Rats Fed a Rosemary Extract Rich in Carnosic Acid," PLoS One, vol. 7, no. 6, art. no. e39773, Jun. 2012, doi: https://doi.org/10.1371/journal.pone.0039773

[58] H. Lou, H. Li, S. Zhang, H. Lu, and Q. Chen, "A Review on Preparation of Betulinic Acid and Its Biological Activities," Molecules., vol. 26, no. 18, art. no. 5583, Sep. 2021, doi: https://doi.org/10.3390/molecules26185583

[59] M. Aswathy, A. Vijayan, U. D. Daimary, S. Girisa, K. V. Radhakrishnan, and A. B. Kunnumakkara, "Betulinic acid: A natural promising anticancer drug, current situation, and future perspectives," J. Biochem. Mol. Toxicol., vol. 36, no. 12, art. no. e23206, Dec. 2022, doi: https://doi.org/10.1002/jbt.23206

[60] P. Singh, Y. Arif, A. Bajguz, and S. Hayat, "The role of quercetin in plants," Plant Physiol. Biochem., vol. 166, pp. 10-19, Sep. 2021, doi: https://doi.org/10.1016/j.plaphy.2021.05.023

[61] Z. Cui, X. Zhao, F. K. Amevor, X. Du, et al., "Therapeutic application of quercetin in aging-related diseases: SIRT1 as a potential mechanism," Front. Immunol., vol. 13, art. 943321, 2022, doi: https://doi.org/10.3389/fimmu.2022.943321

[62] A. Gupta, A. G. Atanasov, Y. Li, N. Kumar, and A. Bishayee, "Chlorogenic acid for cancer prevention and therapy: Current status on efficacy and mechanisms of action," Pharmacol. Res., vol. 186, art. no. 106505, Dec. 2022, doi: https://doi.org/10.1016/j.phrs.2022.106505

[63] L. Wang, X. Pan, L. Jiang, Y. Chu, et al., "The Biological Activity Mechanism of Chlorogenic Acid and Its Applications in Food Industry: A Review," Front. Nutr., vol. 9, art. no. 943911, Jun. 2022, doi: https://doi.org/10.3389/fnut.2022.943911

[64] F. Qoorchi Moheb Seraj, N. Heravi-Daz, A. Soltani, S. S. Ahmadi, et al., "Thymol has anticancer effects in U-87 human malignant glioblastoma cells," Mol. Biol. Rep., vol. 49, no. 10, pp. 9623-9632, Oct. 2022, doi: https://doi.org/10.1007/s11033-022-07867-3

[65] V. Sharma, D. Kumar, K. Dev, and A. Sourirajan, "Anticancer activity of essential oils: Cell cycle perspective," South Afr. J. Bot., vol. 157, pp. 641-647, Jun. 2023, doi: https://doi.org/10.1016/j.sajb.2023.04.031

[66] J. Sharifi-Rad, A. Ozleyen, T. Boyunegmez Tumer, C. Oluwaseun Adetunji, et al., "Natural Products and Synthetic Analogs as a Source of Antitumor Drugs," Biomolecules, vol. 9, no. 11, art. no. 679, Nov. 2019, doi: https://doi.org/10.3390/biom9110679

[67] M. V. Barni, M. J. Carlini, E. G. Cafferata, L. Puricelli, and S. Moreno, "Carnosic acid inhibits the proliferation and migration capacity of human colorectal cancer cells," Oncol. Rep., vol. 27, no. 4, pp. 1041-1048, Apr. 2012, doi: https://doi.org/10.3892/or.2012.1630

[68] J. D. Perales Flores M. J. Verde-Star, J. E. Viveros Valdéz, M. P. Barrón-González, R. A. Garza-Padrón, V. E. Aguirre Arzola, and R. G. Rodriguez Garza, "Actividad antioxidante, tóxica y antimicrobiana de Rosmarinus officinalis, Ruta graveolens y Juglans regia contra Helicobacter pylori," Biotecnia, vol. 25, no. 1, pp. 88-93, Nov. 2022, doi: https://doi.org/10.18633/biotecnia.v25i1.1773

[69] N. Botsoglou, I. Taitzoglou, I. Zervos, E. Botsoglou, M. Tsantarliotou, and P. S. Chatzopoulou, "Potential of long-term dietary administration of rosemary in improving the antioxidant status of rat tissues following carbon tetrachloride intoxication," Food Chem. Toxicol., vol. 48, no. 3, pp. 944-950, Mar. 2010, doi: https://doi.org/10.1016/j.fct.2010.01.004

[70] P. P. Ferrer-Gallego, R. Ferrer-Gallego, R. Roselló, J. B. Peris, A. Guillén, J. Gómez, and E. Laguna, "A new subspecies of Rosmarinus officinalis (Lamiaceae) from the eastern sector of the Iberian Peninsula," Phytotaxa, vol. 172, no. 2, art. no. 61, Jun. 2014, doi: https://doi.org/10.11646/phytotaxa.172.2.1

[71] A. I. Hopia, S.-W. Huang, K. Schwarz, J. B. German, and E. N. Frankel, "Effect of Different Lipid Systems on Antioxidant Activity of Rosemary Constituents Carnosol and Carnosic Acid with and without α-Tocopherol," J. Agric. Food Chem., vol. 44, no. 8, pp. 2030-2036, Jan. 1996, doi: https://doi.org/10.1021/jf950777p

[72] A. Wollinger, É. Perrin, J. Chahboun, V. Jeannot, D. Touraud, and W. Kunz, "Antioxidant activity of hydro distillation water residues from Rosmarinus officinalis L. leaves determined by DPPH assays," Comptes Rendus Chim., vol. 19, no. 6, pp. 754-765, Jun. 2016, doi: https://doi.org/10.1016/j.crci.2015.12.014

[73] W. Wang, N. Wu, Y. G. Zu, and Y. J. Fu, "Antioxidative activity of Rosmarinus officinalis L. essential oil compared to its main components," Food Chem., vol. 108, no. 3, pp. 1019-1022, Jun. 2008, doi: https://doi.org/10.1016/j.foodchem.2007.11.046

[74] F. V. B. Petrolini, R. Lucarini, M. G. de Souza, R. H. Pires, W. R. Cunha, and C. H. Martins, "Evaluation of the antibacterial potential of Petroselinum crispum and Rosmarinus officinalis against bacteria that cause urinary tract infections," Braz. J. Microbiol., vol. 44, no. 3, pp. 829-834, Sep. 2013, doi: https://doi.org/10.1590/s1517-83822013005000061

[75] R. Hamidpour, S. Hamidpour, and G. Elias, "Rosmarinus Officinalis (Rosemary): A Novel Therapeutic Agent for Antioxidant, Antimicrobial, Anticancer, Antidiabetic, Antidepressant, Neuroprotective, Anti-Inflammatory, and Anti-Obesity Treatment," Biomed. J. Sci. Tech. Res., vol. 1, no. 4, Sep. 2017, doi: http://dx.doi.org/10.26717/BJSTR.2017.01.000371

[76] E. Flores-Villa, A. Sáenz-Galindo, A. O. Castañeda-Facio, and R. I. Narro-Céspedes, "Romero (Rosmarinus officinalis L.): su origen, importancia y generalidades de sus metabolitos secundarios," TIP, vol. 23, art. no. e20200266, Nov. 2020, doi: https://doi.org/10.22201/fesz.23958723e.2020.0.266

[77] H. I. Castaño P., G. Ciro G., J. E. Zapata M., and S. L. Jiménez R., "Bactericidal activity of ethanolic leaf extract and leaf essential oil of Rosmarinus officinalis L. on some foodborne bacteria," Vitae, vol. 17, no. 2, pp. 149-154, Jul. 2010, doi: https://doi.org/10.17533/udea.vitae.6334

[78] X. K. Solano Solano, M. I. Zambrano Gutiérrez, "Inhibición del Streptococcus mutans, mediante el uso de extracto acuoso y oleoso de Rosmarinus officinalis "romero"," Rev. Odontol., vol. 19, no. 2, pp. 29-34, 2016. [Online]. Available: https://dialnet.unirioja.es/servlet/articulo?codigo=5815882

[79] M. A. Montero-Recalde, J. A. Martinez-Jimenéz, D. F. Avilés-Esquivel, E. L. Valle-Velástegui, and N. D. P. Pazmiño-Miranda, "Efecto antimicrobiano del extracto crudo oleoso de Rosmarinus Officinalis sobre cepa de Escherichia coli," J. Selva Andina Biosphere, vol. 5, no. 2, pp. 168-175, Nov. 2017, doi: https://doi.org/10.36610/j.jsab.2017.050200168

[80] N. R. Farnsworth, O. Akerele, A. S. Bingel, D. D. Soejarto, and Z. Guo, "Medicinal plants in therapy," Bull. World Health Organ., vol. 63, no. 6, pp. 965-981, 1985. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2536466/pdf/bullwho00089-0002.pdf

[81] O. V. Filiptsova, L. V. Gazzavi-Rogozina, I. A. Timoshyna, O. I. Naboka, Ye. V. Dyomina, and A. V. Ochkur, "The essential oil of rosemary and its effect on the human image and numerical short-term memory," Egypt. J. Basic Appl. Sci., vol. 4, no. 2, pp. 107-111, Jun. 2017, doi: https://doi.org/10.1016/j.ejbas.2017.04.002

[82] M. A. El-Desouky, M. H. Mahmoud, B. Y. Riad, and Y. M. Taha, "Nephroprotective effect of green tea, rosmarinic acid and rosemary on N-diethylnitrosamine initiated and ferric nitrilotriacetate promoted acute renal toxicity in Wistar rats," Interdiscip. Toxicol., vol. 12, no. 2, pp. 98-110, Oct. 2019, doi: https://doi.org/10.2478/intox-2019-0012

[83] S. Makaremi, A. Ganji, A. Ghazavi, and G. Mosayebi, "Inhibition of tumor growth in CT-26 colorectal cancer-bearing mice with alcoholic extracts of Curcuma longa and Rosmarinus officinalis," Gene Rep., vol. 22, art. no. 101006, Mar. 2021, doi: https://doi.org/10.1016/j.genrep.2020.101006

[84] L. M. Muñoz Centeno, "Plantas medicinales españolas. Rosmarinus officinalis L. (Lamiaceae) (romero)," Stud. Bot., vol. 21, 2002. [Online]. Available: https://revistas.usal.es/historico/index.php/0211-9714/article/view/6111

[85] I. Borrás Linares, D. Arráez-Román, M. Herrero, E. Ibáñez, A. Segura-Carretero, and A. Fernández-Gutiérrez, "Comparison of different extraction procedures for the comprehensive characterization of bioactive phenolic compounds in Rosmarinus officinalis by reversed-phase high-performance liquid chromatography with diode array detection coupled to electrospray time-of-flight mass spectrometry," J. Chromatogr. A, vol. 1218, no. 42, pp. 7682-7690, Oct. 2011, doi: https://doi.org/10.1016/j.chroma.2011.07.021

[86] M. Kumar, M. D. Barbhai, S. Puranik, Radha, et al., "Combination of green extraction techniques and smart solvents for bioactives recovery," TrAC Trends Anal. Chem., vol. 169, art. no. 117286, Dec. 2023, doi: https://doi.org/10.1016/j.trac.2023.117286

[87] S. Oubannin, L. Bijla, M. N. Ahmed, M. Ibourki, et al., "Recent advances in the extraction of bioactive compounds from plant matrices and their use as potential antioxidants for vegetable oils enrichment," J. Food Compos. Anal., vol. 128, art. no. 105995, Apr. 2024, doi: https://doi.org/10.1016/j.jfca.2024.105995

[88] F. Chemat, M. A. Vian, A.-S. Fabiano-Tixier, M. Nutrizio, et al., "A review of sustainable and intensified techniques for extraction of food and natural products," Green Chem., vol. 22, no. 8, pp. 2325-2353, 2020, doi: https://doi.org/10.1039/C9GC03878G

[89] P. R. More, A. R. Jambrak, and S. S. Arya, "Green, environment-friendly and sustainable techniques for extraction of food bioactive compounds and waste valorization," Trends Food Sci. Technol., vol. 128, pp. 296-315, Oct. 2022, doi: https://doi.org/10.1016/j.tifs.2022.08.016

[90] W. T. Richards and A. L. Loomis, "The chemical effects of high frequency sound waves I. A preliminary survey," J. Am. Chem. Soc., vol. 49, no. 12, pp. 3086-3100, Dec. 1927, doi: https://doi.org/10.1021/ja01411a015

[91] K. S. Suslick, "The Chemical Effects of Ultrasound," Sci. Am., vol. 260, no. 2, pp. 80-86, feb. 1989, doi: https://doi.org/10.1038/scientificamerican0289-80

[92] N. Pokhrel, P. K. Vabbina, and N. Pala, "Sonochemistry: Science and Engineering," Ultrason. Sonochem., vol. 29, pp. 104-128, Mar. 2016, doi: https://doi.org/10.1016/j.ultsonch.2015.07.023

[93] L. E. Robles-Ozuna and L. A. Ochoa-Martínez, "Ultrasonido y sus aplicaciones en el procesamiento de alimentos," vol. 13, no. 2, pp. 109-122, 2012. [Online]. Available: https://www.redalyc.org/articulo.oa?id=81325441002

[94] M. Islam, S. Malakar, M. V. Rao, N. Kumar, and J. K. Sahu, "Recent advancement in ultrasound-assisted novel technologies for the extraction of bioactive compounds from herbal plants: a review," Food Sci. Biotechnol., vol. 32, no. 13, pp. 1763-1782, Nov. 2023, doi: https://doi.org/10.1007/s10068-023-01346-6

[95] D. Y. Hoo, Z. L. Low, D. Y. S. Low, S. Y. Tang, S. Manickam, K. W. Tan, Z. H. Ban, "Ultrasonic cavitation: An effective cleaner and greener intensification technology in the extraction and surface modification of nanocellulose," Ultrason. Sonochem., vol. 90, art. no. 106176, Nov. 2022, doi: https://doi.org/10.1016/j.ultsonch.2022.106176

[96] M. Ramić, S. Vidović, Z. Zeković, J. Vladić, A. Cvejin, and B. Pavlić, "Modeling and optimization of ultrasound-assisted extraction of polyphenolic compounds from Aronia melanocarpa by-products from filter-tea factory," Ultrason. Sonochem., vol. 23, pp. 360-368, Mar. 2015, doi: https://doi.org/10.1016/j.ultsonch.2014.10.002

[97] N. A. Al-Dhabi, K. Ponmurugan, and P. Maran Jeganathan, "Development and validation of ultrasound-assisted solid-liquid extraction of phenolic compounds from waste spent coffee grounds," Ultrason. Sonochem., vol. 34, pp. 206-213, Jan. 2017, doi: https://doi.org/10.1016/j.ultsonch.2016.05.005

[98] K. Kumar, S. Srivastav, and V. S. Sharanagat, "Ultrasound assisted extraction (UAE) of bioactive compounds from fruit and vegetable processing by-products: A review," Ultrason. Sonochem., vol. 70, art. no. 105325, Jan. 2021, doi: https://doi.org/10.1016/j.ultsonch.2020.105325

[99] C. Wen, J. Zhang, H. Zhang, C. S. Dzah, et al., "Advances in ultrasound assisted extraction of bioactive compounds from cash crops - A review," Ultrason. Sonochem., vol. 48, pp. 538-549, Nov. 2018, doi: https://doi.org/10.1016/j.ultsonch.2018.07.018

[100] C. S. Dzah, Y. Duan, H. Zhang, C. Wen, J. Zhang, G. Chen, H. Ma, "The effects of ultrasound assisted extraction on yield, antioxidant, anticancer and antimicrobial activity of polyphenol extracts: A review," Food Biosci., vol. 35, art. no. 100547, Jun. 2020, doi: https://doi.org/10.1016/j.fbio.2020.100547

[101] I. M. Yusoff, Z. Mat Taher, Z. Rahmat, and L. S. Chua, "A review of ultrasound-assisted extraction for plant bioactive compounds: Phenolics, flavonoids, thymols, saponins and proteins," Food Res. Int., vol. 157, art. no. 111268, Jul. 2022, doi: https://doi.org/10.1016/j.foodres.2022.111268

[102] A. C. Feihrmann, N. M. da Silva, A. R. de Marins, M. Antônio Matiucci, et al., "Ultrasound-assisted extraction and encapsulation by spray drying of bioactive compounds from Tradescantia zebrina leaves," Food Chem. Adv., vol. 4, art. no. 100621, Jun. 2024, doi: https://doi.org/10.1016/j.focha.2024.100621

[103] R. Biswas, A. Sarkar, M. Alam, M. Roy, and M. M. Mahdi Hasan, "Microwave and ultrasound-assisted extraction of bioactive compounds from Papaya: A sustainable green process," Ultrason. Sonochem., vol. 101, art. no. 106677, Dec. 2023, doi: https://doi.org/10.1016/j.ultsonch.2023.106677

[104] A. Olfat, T. Mostaghim, S. Shahriari, and M. Salehifar, "Extraction of bioactive compounds of Hypnea flagelliformis by ultrasound-assisted extraction coupled with natural deep eutectic solvent and enzyme inhibitory activity," Algal Res., vol. 78, art. no. 103388, Mar. 2024, doi: https://doi.org/10.1016/j.algal.2023.103388

[105] A. Palma, M. Ruiz-Montoya, M. J. Díaz, I. Giráldez, and E. Morales, "Optimization of bioactive compounds by ultrasound extraction and gas chromatography - mass spectrometry in fast-growing leaves," Microchem. J., vol. 193, art. no. 109231, Oct. 2023, doi: https://doi.org/10.1016/j.microc.2023.109231

[106] K. S. L. Miki, A. P. Dresch, M. Cavali, A. P. da Silva, et al., "Influence of drying methods in the ultrasound-assisted extraction of bioactive compounds from Byrsonima crassifolia to evaluate their potential antitumor activity," Food Humanity, vol. 2, art. no. 100242, May 2024, doi: https://doi.org/10.1016/j.foohum.2024.100242

[107] P. Petchimuthu, G. B. Sumanth, S. Kunjiappan, S. Kannan, S. R. K. Pandian, and K. Sundar, "Green extraction and optimization of bioactive compounds from Solanum torvum Swartz. using ultrasound-aided solvent extraction method through RSM, ANFIS and machine learning algorithm," Sustain. Chem. Pharm., vol. 36, art. no. 101323, Dec. 2023, doi: https://doi.org/10.1016/j.scp.2023.101323

[108] H. Koraqi, A. Trajkovska Petkoska, W. Khalid, N. Kumar, and S. Pareek, "Optimization of experimental conditions for bioactive compounds recovery from raspberry fruits (Rubus idaeus L.) by using combinations of ultrasound-assisted extraction and deep eutectic solvents," Appl. Food Res., vol. 3, no. 2, art. no. 100346, Dec. 2023, doi: https://doi.org/10.1016/j.afres.2023.100346

[109] S. Albu, E. Joyce, L. Paniwnyk, J. P. Lorimer, and T. J. Mason, "Potential for the use of ultrasound in the extraction of antioxidants from Rosmarinus officinalis for the food and pharmaceutical industry," en Ultrason. Sonochem., vol. 11, no. 3-4, pp. 261-265, May 2004, doi: https://doi.org/10.1016/j.ultsonch.2004.01.015

[110] L. Paniwnyk, H. Cai, S. Albu, T. J. Mason, and R. Cole, "The enhancement and scale up of the extraction of anti-oxidants from Rosmarinus officinalis using ultrasound," Ultrason. Sonochem., vol. 16, no. 2, pp. 287-292, Feb. 2009, doi: https://doi.org/10.1016/j.ultsonch.2008.06.007

[111] M. Nicolai, P. Pereira, R. F. Vitor, C. P. Reis, A. Roberto, and P. Rijo, "Antioxidant activity and rosmarinic acid content of ultrasound-assisted ethanolic extracts of medicinal plants," Meas. J. Int. Meas. Confed., vol. 89, pp. 328-332, Jul. 2016, doi: https://doi.org/10.1016/j.measurement.2016.04.033

[112] X. Zhong, X. Wang, N. Zhou, J. Li, et al., "Chemical characterization of the polar antibacterial fraction of the ethanol extract from Rosmarinus officinalis," Food Chem., vol. 344, art. no. 128674, May 2021, doi: https://doi.org/10.1016/j.foodchem.2020.128674

[113] R. S. Pizani, J. Viganó, L. S. Contieri, M. M. Strieder, et al., "New selective and sustainable ultrasound-assisted extraction procedure to recover carnosic and rosmarinic acids from Rosmarinus officinalis by sequential use of bio-based solvents," Food Chem., vol. 435, art. no. 137540, Mar. 2024, doi: https://doi.org/10.1016/j.foodchem.2023.137540

[114] G. Chisha, C. Li, L. Xiao, B. Wang, Y. Chen, and Z. Cui, "Multiscale mechanism exploration and experimental optimization for rosmarinic acid extraction from Rosmarinus officinalis using natural deep eutectic solvents," Ind. Crops Prod., vol. 188, art. no. 115637, Nov. 2022, doi: https://doi.org/10.1016/j.indcrop.2022.115637

[115] A. Ali, B. L. Chua, Y. H. Chow, and C. H. Chong, "Development and characterisation of novel terpenoid-based hydrophobic deep eutectic solvents for sustainable extraction of bioactive antioxidants from Rosmarinus officinalis L," J. Mol. Liq., vol. 388, art. no. 122792, Oct. 2023, doi: https://doi.org/10.1016/j.molliq.2023.122792

[116] S. S. Ayyildiz, E. Pelvan, and B. Karadeniz, "Optimization of accelerated solvent extraction, ultrasound assisted and supercritical fluid extraction to obtain carnosol, carnosic acid and rosmarinic acid from rosemary," Sustain. Chem. Pharm., vol. 37, art. no. 101422, Feb. 2024, doi: https://doi.org/10.1016/j.scp.2023.101422

[117] C. Caleja, L. Barros, M. A. Prieto, M. F. Barreiro, M. B. P. P. Oliveira, and I. C. F. R. Ferreira, "Extraction of rosmarinic acid from Melissa officinalis L. by heat-, microwave- and ultrasound-assisted extraction techniques: A comparative study through response surface analysis," Sep. Purif. Technol., vol. 186, pp. 297-308, Oct. 2017, doi: https://doi.org/10.1016/j.seppur.2017.06.029

[118] M. Jacotet-Navarro, N. Rombaut, A.-S. Fabiano-Tixier, M. Danguien, A. Bily, and F. Chemat, "Ultrasound versus microwave as green processes for extraction of rosmarinic, carnosic and ursolic acids from rosemary," Ultrason. Sonochem., vol. 27, pp. 102-109, Nov. 2015, doi: https://doi.org/10.1016/j.ultsonch.2015.05.006

[119] M. Bellumori, M. Innocenti, A. Binello, L. Boffa, N. Mulinacci, and G. Cravotto, "Selective recovery of rosmarinic and carnosic acids from rosemary leaves under ultrasound- and microwave-assisted extraction procedures," Comptes Rendus Chim., vol. 19, no. 6, pp. 699-706, Apr. 2016, doi: https://doi.org/10.1016/j.crci.2015.12.013

[120] D. Tungmunnithum, L. Garros, S. Drouet, S. Renouard, E. Lainé, and C. Hano, "Green Ultrasound Assisted Extraction of trans Rosmarinic Acid from Plectranthus scutellarioides (L.) R.Br. Leaves," Plants, vol. 8, no. 3, art. no. 50, Feb. 2019, doi: https://doi.org/10.3390/plants8030050

[121] G. Zu, R. Zhang, L. Yang, C. Ma, Y. Zu, W. Wang, C. Zhao, "Ultrasound-Assisted Extraction of Carnosic Acid and Rosmarinic Acid Using Ionic Liquid Solution from Rosmarinus officinalis," Int. J. Mol. Sci., vol. 13, no. 9, pp. 11027-11043, Sep. 2012, doi: https://doi.org/10.3390/ijms130911027

[122] A. M. Hrebień-Filisińska and G. Tokarczyk, "The Use of Ultrasound-Assisted Maceration for the Extraction of Carnosic Acid and Carnosol from Sage (Salvia officinalis L.) Directly into Fish Oil," Molecules, vol. 28, no. 16, art. no. 6094, Aug. 2023, doi: https://doi.org/10.3390/molecules28166094

[123] N. Dhouibi, S. Manuguerra, R. Arena, C. M. Messina, et al., "Impact of the Extraction Method on the Chemical Composition and Antioxidant Potency of Rosmarinus officinalis L. Extracts," Metabolites, vol. 13, no. 2, art. no. 290, Feb. 2023, doi: https://doi.org/10.3390/metabo13020290