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Rosemary, the beneficial chemistry of a garden herb

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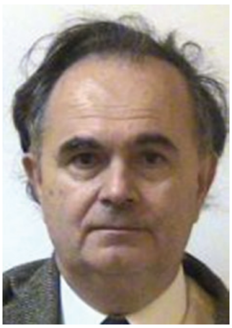

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ABSTRACT

*The major natural products that are present in the garden herb, rosemary (*Rosmarinus officinalis*) including the mono di- and triterpenoid, flavonoid and phenolic constituents together with their biological activity as anti-microbial, anti-oxidant, anti-inflammatory, memory-enhancing and tumour-inhibitory agents, are reviewed.*

Keywords: *Rosmarinus officinalis, cineole, carnosol, rosmarinic acid, anti-oxidant*

"There's rosemary, that's for remembrance; pray, love remember"
(Ophelia in Hamlet, Act IV Scene 5, Shakespeare)

Introduction

Rosemary is a garden herb originating from the Mediterranean whose valuable beneficial properties have been known for many centuries. However the chemical constituents which contribute to these properties, have only been identified over the last 50 years. The Egyptians buried sprigs of rosemary in the Pharaoh's tombs whilst both the Ancient Greeks and Romans regarded it as a sacred plant. The effect of the plant in enhancing memory, led to the ancient custom of using it as a symbol of faithfulness and remembrance at weddings and funerals. There is an old custom of casting a sprig of rosemary onto a coffin before it is lowered into the grave. Rosemary is sometimes used along with lavender to prevent moth damage. Its antiseptic properties accounted for uses in preserving food, particularly meat, whilst rosemary branches were burnt in medieval hospitals as a fumigant and possibly to increase the sense of well-being of the patients – hence the old' French name of 'incensiere' for the plant. The use of rosemary for the treatment of a variety of ailments figures in many herbal remedies[1].

Rosemary, *Rosmarinus officinalis,* is a member of the Lamiaceae. It is a perennial evergreen shrub with characteristic narrow leaves and a small blue flower (Figure 1). The structure of the flower with its tongue-like shape is typical of the Lamiaceae and reflects the old name, Labiatae, for this family of plants. It grows best in rather light, dry and sandy soil.

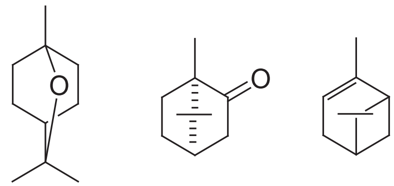
Rosemary belongs to the same sub-family, the Nepetoideae, as the Salvias, *e.g. S. officinalis* (sage) and *S. miltiorrhiza* (tan-shen). Consequently it is not surprising that there are similarities in their constituents. These plants are known for their mono-, di- and tri-terpenoid, flavonoid and phenolic constituents but, on the whole, they are not known as alkaloid-bearing plants.

Figure 1 *Rosmarinus officinalis prostrates.*

Although rosemary was originally a Mediterranean plant, it is now grown in many temperate climates including South and North America, parts of the Far East and in Europe. It is not just an ornamental plant but is grown as a commercial herb. Several products are obtained from the plant including the 'essential oil' arising from distillation or supercritical carbon dioxide extraction of the flowers and leaves, a tincture arising from aqueous ethanolic extraction of the leaves and twigs and finally the crushed intact plant which is sold as a culinary herb. Each of these contains a range of phytochemicals and has different uses[2–5]. These constituents are discussed in the following sections.

The composition of the essential oil

The volume of essential oil obtained from rosemary plants varies according to the method of extraction such as hydrodistillation or supercritical CO_2 extraction as well as with the age of the plant and season of harvest but is typically 10 mL kg^{-1} of dry plant. The major monoterpenoids (Figure 2) are typically 1:8-cineole (also known as eucalyptol) (**1**), camphor (**2**), α-pinene (**3**) with lesser amounts of other well-known monoterpenoids including terpineol, limonene, *p*-cymene, camphene and borneol. The proportions of these vary depending on the chemotype, the cultivation and climatic conditions, the season and country of origin[6–10]. In recent years, there have been many gas chromatographic:mass spectroscopic analyses of the essential oils from rosemary plants that were grown, for example in Italy, Spain, Morocco,



1 2 3

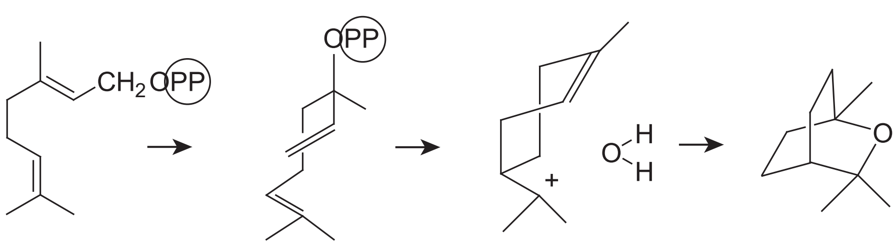
Figure 2 *The major monoterpenoids.*

Tunisia, the Balkans and Brazil. As many as 75 constituents have been detected. There appear to be some distinct chemotypes including those in which either cineole, camphor or α-pinene predominate. These variations, of course, affect the quality of the essential oil (Figure 3).

The biosynthesis of the monoterpenes has been thoroughly studied using many different plants and enzyme-systems derived from them. Early experiments on the biosynthesis of monoterpenes such as cineole used[11] rosemary as an experimental medium. These showed for the first time that [1-^{14}C]-geranyl diphosphate (**4**) was specifically incorporated into a cyclic monoterpene. Subsequent biosynthetic experiments[12–16] using other plants established a sequence *via* the cyclisation of the tertiary linalool diphosphate (**5**) to a carbocyclic α-terpinyl cation (**6**) which was then hydrated to form the ether of cineole (**1**).

Although cineole is a cyclic ether, which would normally be regarded as relatively unreactive, various aspects of its chemistry have been investigated including studies of structure : odour relationships[17].

Unlike plants of the Asteraceae (Compositae) which are well-known for their production of sesquiterpenoid lactones, the Lamiaceae do not produce substantial amounts of highly oxygenated sesquiterpenes. Only small amounts of sesquiterpene hydrocarbons such as humulene, cedrene and caryophyllene and a few oxygenated compounds such as caryophyllene oxide, have been found in the essential oil of rosemary[10,18].



4 5 6 1

PP = diphosphate

Figure 3

The diterpenoids of rosemary

Many, but not all, of the anti-oxidant properties of rosemary are associated with the presence of the diterpenoids, principally carnosic acid (**7**) and carnosol (**8**) (Figure 4). Carnosol was originally isolated[19] as a bitter principle from a related sage, *S. carnosa.* Subsequently in another investigation, picrosalvin was isolated[20] from *S. officinalis, S. triloba* and *R. officinalis* but the wrong structure was assigned to it. The identity of carnosol and picrosalvin was established[21] and a revised structure was proposed on the basis of NMR measurements and a relationship with a known diterpenoid, ferruginol. Carnosic acid was formed by hydrogenolysis of the lactone of carnosol. An anomalous 'alkaloid' rosmaricine had been described as a constituent of rosemary but it was shown[22] to be an artefact in which the amino group at C-7 had been introduced from the ammonia which was used in the isolation procedure. Various other aromatic abietanes have been isolated[23–29] from rosemary in a number of later investigations. These compounds are similar to the abietanes such as the tanshinones which have been isolated from related *Salvia* species. Typically they possess oxygen functions at C-11, C-12 and C-20 and they vary in the nature of the substituents at C-6 and C-7. The oxidation of C-20 to a carboxylic acid is relatively unusual amongst

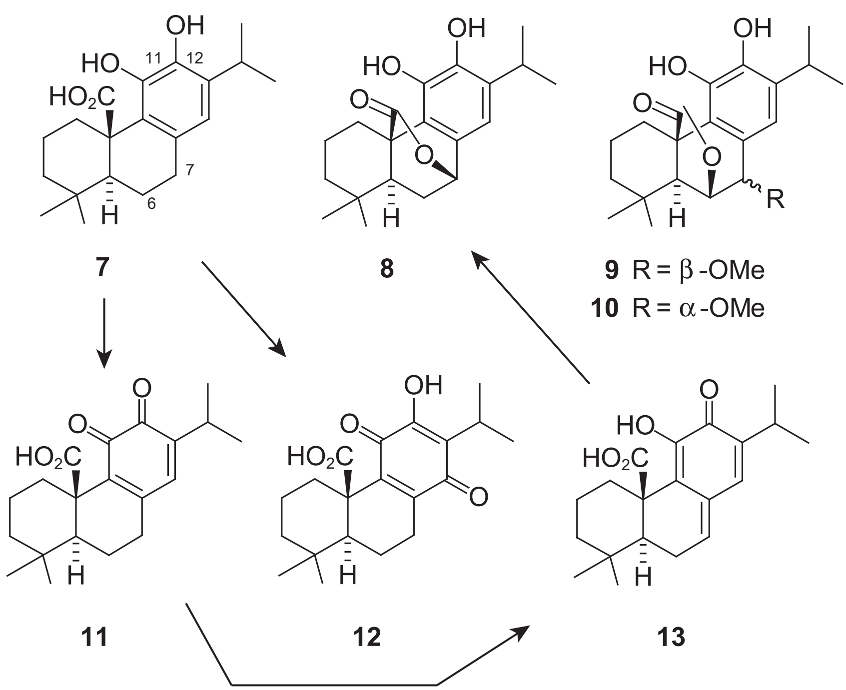


Figure 4 *Carnosic acid (7) and carnosol (**8**)*

the tricyclic diterpenes. Whereas carnosol (**8**) is a 20→7-δ-lactone, rosmanol is a 20→6-γ-lactone with a 7α-hydroxyl group. 12-Methoxycarnosic acid and a number of quinones including the *o*-quinones, rosmaquinones A and B (**9**, **10**),a ring A *seco* compound (3,4-seco-hinokiol), a ring B seco-dialdehyde, rosmadial and rosmaridiphenol (11,12-dihydroxy-8,11,13-icetexatrien-1-one) are amongst the other diterpenoid constituents. Procedures have been described for isolating the lipid soluble phenolic diterpenes of rosemary and for determining their concentration[30–33].

A characteristic feature of these anti-oxidant diterpenoids is the presence of the 11,12-*o*-catechol. A study of the anti-oxidant mechanism involving carnosic acid (**7**) has led[34,35] to the identification of an *ortho-* (**11**) and *para*-quinone (**12**). The formation of carnosol (**8**), the 7-hydroxy-, 7-methoxy and rosmaricine together with other degradation products, can then be rationalised in terms of the formation of these quinones and nucleophilic addition to their tautomeric quinone methides (*e.g.* **13**). Since the *o*-catechol is regenerated in carnosol (**8**), it also behaves as an anti-oxidant. Tentative structures have been proposed for some metabolites in which the C-20 carbonyl group has been removed.

There has been considerable interest[36] in the biosynthesis of the diterpenes by cyclisation of geranylgeranyl diphosphate (**14**) *via* the bicyclic copalyl diphosphate (**15**) to form the tricyclic miltiradiene (**16**) which is then oxidised to the phenol, ferruginol (**17**) (Figure 5). Two genes which control the formation of the synthases for these cyclisations have been characterised[37] in rosemary.

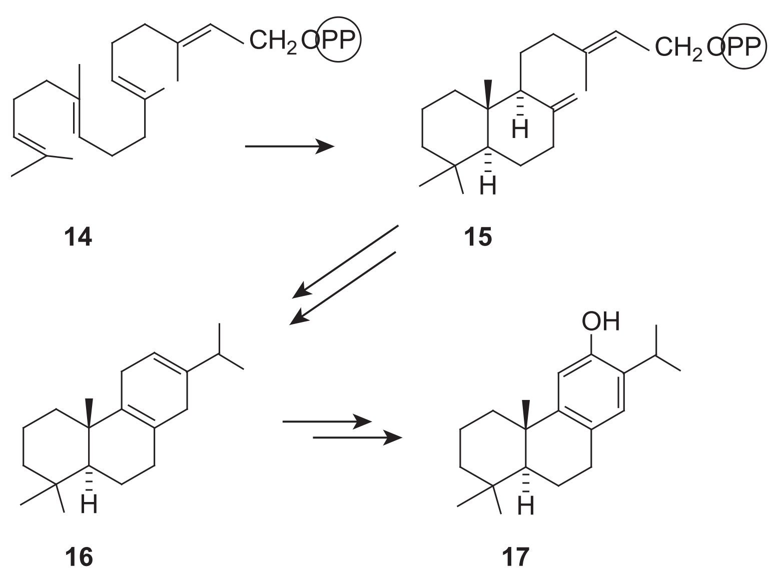
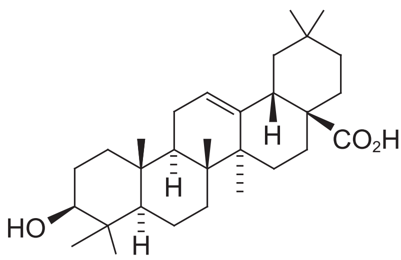


Figure 5

The triterpenes of rosemary

The triterpenes which have been obtained[11,18,38–40] from rosemary include the well-known squalene, 3-epi-α-amyrin, ursolic, oleanolic (**18**) and micromeric acids as well as rofficerone, betulin (**19**), betulinic acid (**20**) and 23-hydroxybetulinic acid (Figure 6). The anti-inflammatory and tumour inhibitory activity of rosemary has been associated with the presence of these triterpenes.



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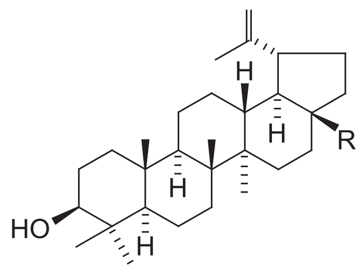
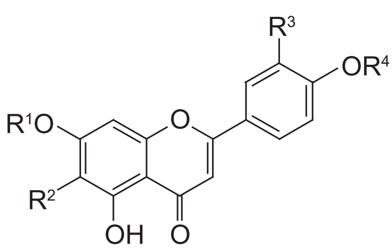


19 R = CH_2OH
20 R = CO_2H

Figure 6

The flavonoid and phenolic constituents of rosemary

Extraction of rosemary with polar solvents such as aqueous ethanol, has led to the isolation of more highly hydroxylated compounds including some flavonoids and their glycosides together with rosmarinic acid (**25**) and other caffeic acid esters. These widespread natural products are also powerful anti-oxidants. The major compounds which have been isolated[41–44] from rosemary include genkwanin (**21**), diosmin (**22**) and cirsimaritin (**23**) (Figure 7). A biogenetic relationship linking these compounds to the parent flavanone, naringenin (**24**) has been proposed. Key steps involve the dehydrogenation of the flavanone to



21 R^1 = Me, R^2 = R^3 = R^4 = H
22 R^1 = R^2 = H, R^3 = OH, R^4 = Me
23 R^1 = Me, R^2 = OMe, R^3 = R^4 = H

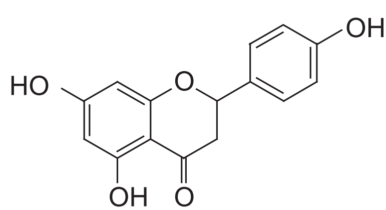


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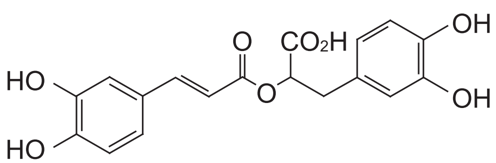
Figure 7

the flavone, hydroxylation at C-3' and the methylation and glycosylation of different hydroxyl groups. In some cases the sugars are esterified not just with acetate units but also with ferulic and coumaric acids.

Rosmarinic acid (**25**) which is an ester of caffeic acid and 3,4-dihydroxyphenyl lactic acid, was first isolated from rosemary in 1958 and is a typical constituent of the Nepetoideae sub-family of the Lamiaceae[45,46] (Figure 8). Like the diterpenoids carnosic acid and carnosol, rosmarinic acid possesses *ortho*-dihydroxyphenols which are readily oxidised to the *o*-quinones and it behaves as a powerful radical scavenging agent. The biosynthesis of rosmarinic acid from phenylalanine and tyrosine *via* coumaric acid and caffeic acid has been established using enzyme preparations from another member of the Lamiaceae, *Coleus blumei.*



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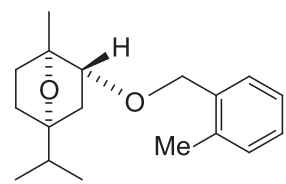

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Figure 8

The biological activity of the constituents of rosemary

Although many of the reports of the biological activity of rosemary have not linked these with specific constituents carnosic acid (**7**), carnosol (**8**), rosmarinic acid (**25**) and the flavonoids have been regularly associated[25,47–53] with the anti-oxidant, anti-microbial and anti-proliferative activity of rosemary. They may account for the use of rosemary in preserving cooked meat such as lamb and poultry. Various quinonoid carnosol metabolites have been detected in these studies[54]. A carnosic acid $20 \rightarrow 11$ lactone and various C-12 ethers have a gastroprotective effect by inhibiting lipid oxidation[55,56]. The triterpenes that are present also have an anti-inflammatory and anti-cancer activity[57].

The essential oil from rosemary has been shown[58,59] to affect cognition and mood and these effects have been attributed to the presence of cineole (**1**) and α-pinene (**3**). Rosemary has an inhibitory effect on acetylcholine esterase[60] which is involved in the metabolism of acetylcholine. Cineole (**1**), carnosol (**8**) and betulinic acid (**20**) have all been associated with the anti-depressant activity of rosemary[59].

Typical of members of the Lamiaceae, such as the mints, the essential oil from rosemary has a marked allelopathic effect preventing the germination of seeds and inhibiting the growth of competitive plants[61,62]. The volatile 1:4- and 1:8-cineoles have been shown to be responsible for this effect. This has led to the development of a novel pre-emergence herbicide, cinmethylin (**26**).

Camphor (**2**) which is also present in the essential oil, is a known acaricide and may be responsible for the activity of the essential oil of rosemary against various mites including the Varroa mite found on bees and the spider mite *Tetranychus urticae* which is a serious pest in greenhouses[63,64]. Birds such as starlings, when re-using an old nest will line it with herbal material to reduce the impact of parasites.

In conclusion the phytochemical studies on rosemary which have been carried out over the last 50 years, have provided a chemical rationale for the biological activity of this herb which has been used for many centuries. Some of these biological activities have been associated with the presence of particular compounds whose structures may provide potential leads for the development of novel drugs. Not only is this herb readily available but it is also worth noting that many of these structures are closely related to other natural products that are readily available from other sources and which could provide the starting materials for structure : activity studies. This common garden herb has proved to be a treasure trove of beneficial natural products.

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