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Review

Secondary metabolites of the argan tree (Morocco) may have disease prevention properties

Khallouki F, Spiegelhalder B, Bartsch H and Owen RW*

Division of Toxicology and Cancer risk Factors, Im Neunheimer Feld, 280, German Cancer Research Center (DKFZ), Heidelberg, Germany

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The argan tree (*Argania spinosa* L. Skeels) is native to Morocco, where after the Holly oak it constitutes the second most common tree in the country. Recent studies suggest that dietary argan oil, an endemic seed oil from argan fruits, may have a relevant role in disease prevention, and its consumption could protect against atherosclerosis and cancer. Unfortunately, in less than a century, more than a third of the forest has disappeared. It is therefore imperative to improve the tree's production potential so that it can regain its key position in the agricultural systems of the region. On the basis of ethnobotanical knowledge, researchers are screening metabolites of this rare plant to identify bioactive compounds for the development of new therapeutic agents and food supplements. This includes studies on secondary metabolites with chemopreventive activities. In this review, a complete outline of components (triglycerides, unsaponifiable, phenolic antioxidants and aroma constituents) are described. Finally, a discussion of the biological functions of the polar and non-polar *A. spinosa* products which have been evaluated using a range of *in vitro* bioassays are described.

Key words: *Argania spinosa*, fatty acids, sterols, vitamine E, γ-tocopherols, triterpenes, saponins, nutritional,chemopreventive properties

INTRODUCTION

The argan (Figure 1) tree (*Argania spinosa*) is an oleaginous tree indigenous to the Sahara dessert, the Anti-Atlas and the High Atlas Mountains of southwestern Morocco. According to Boukhobza et al. (1988), the appearance of argan trees dates from the tertiary era, when it was widespread throughout Morocco. Etymologically, the words argan (the tree) come from the Berber word `' arjân' which, derives from the `' rajnah' ' which, means in Berber dialect “to remain locked up” in a limited place. In fact the argan tree is endemic to Morocco.

Corresponding Author E-mail : r.owen@dkfz-heidelberg.de.

The argan tree belongs to the family of Sapotaceae which contains eight genera: *Syderoxylon*, *Tsebona*, *Bumelia*, *Argania*, *Chrysophyllum*, *Pouteria*, *calocapum* and *Pycnandra*. The genus *Argania* consists of only one endemic species: *Argania spinosa* (syn. *Argania syderoxylon* L, *Sideroxylon spinosum* L Elaerandron argan Retz). The argan tree can reach heights of up to 10 meters and survives for about 200 years. These trees have an amazing ability to adapt to the climate of southwestern Morocco. A thorny, evergreen tree with small, green, lanceolate leaves; sheds its leaves and becomes dormant during severe droughts. The dormancy period, which can last for several years, is broken when the trees sense moisture in the air and refoliation begins.

The argan tree plays a vital role in maintaining the ecological balance where its roots grow deep in search of

Figure 1. Argan tree (A), fruit (B) and seeds (C).

water and thus help retain the soil, preventing erosion and limiting the advance of the desert. Under and around the trees, flora and fauna thrive and in turn create an eco-diversity crucial to this region. Today, the Argan Region is about 820,000 hectares, or 70% of the wooded surface in south-western Morocco where annual precipitations do not exceed 300 mm, and like most tropical fruit trees, it is multi-purpose. Mainly women carry out collection, local processing and trading activities. However, in less than a century, more than a third of the argan forest has disappeared due to demand for high quality charcoal and conversion of land to agriculture.

The forest supports more than 3 million Berbers, the original inhabitants of Morocco, by providing them with wood for heating, feed for livestock, and edible oil for cooking, cosmetic and medicinal purposes. The press cake is used as raw material by the cosmetic industry, and is also used as an energy supplement in bovine feed.

Argan oil is believed to have strong anti-oxidative properties, especially those that affect the skin where the

oil is often used to combat physiological aging and drying of skin; to neutralize free radicals and conjunctive tissue; to promote softer and stronger hair; and to strengthen breaking and unhealthy nails. The oil is used in the treatment of children's pimples and more particularly in juvenile acne, and is used to treat wrinkles, light wounds and chicken pox pustules. It is also prescribed against rheumatism, choleresis, and hypocholesteraemia (Charrouf et al., 1999).

FRUITS

The fruits are distinguishable in form (spindle-shaped, oval, drop, round or globulous) (Jaccard, 1925). They are green when unripe, and turn bright yellow at maturity. The pericarp comprises three layers, the exocarp (skin), mesocarp (outer pulp) and endocarp (an ovate hard-shelled nut, which encloses the fleshy albumen or argan kernel [the endosperm] which contains oil). The oil content depends on genotype and environment and ranges from 50-56 g/100 g of the kernal (Nerd et al., 1994).

Table 1. Positional distribution of fatty acids (%) in argan oil (Khallouki, 2003b).

Type of oil	Food variety	Aesthetic variety
Sn-1.3		
Saturated fatty acids	20,5 %	20,7 %
Oleic acid	28,9 %	30,3 %
Vascenic acid	1%	0,9 %
Linoleic acid	18,4 %	19,4 %
Sn-2		
Oleic acid	17,2 %	15,3 %
Linoleic acid	13,9 %	13,3

CHEMISTRY OF ARGAN OIL

Triglycerides

Like all oils, triacylglycerols (TAGs) are the major constituents of argan oil. Over 99% of argan oil consists of mixtures of TAGs, i.e. glycerol molecules, each esterified with three fatty acids. During oil extraction from the kernal, the hydrophobic TAGs attract other fat- or oil-soluble cellular components. These are the minor components of argan oil such as, triterpenes, sterols, pigments, tocopherols and trace metals. Other components in argan oil are the metabolites from the biosynthesis of TAGs and products of lipolytic activity. These include the monoacylglycerols, diacylglycerols and free fatty acids. 13C NMR methodologies, which are used to characterize oils (Mannina et al., 1999) have been conducted to locate the triglyceridic regiospecificity of the profile of argan oil and the results of this study (Khallouki, 2003) (Table 1), indicated that the method is more convenient and less time consuming. It shows that saturated fatty acids (palmitic or stearic) generally substitute the glycerol extremities (Sn-1 and Sn-3) while oleic acid generally esterifies the glycerol secondary alcohol (Sn-3). Linoleic acid is distributed equally at any of the three positions (manuscript in preparation).

Fatty acids of argan oil

The major fatty acids in argan oil are oleic, linoleic, stearic, and palmitic acids (Charrouf et al., 1999; Khallouki, 2003; Khallouki et al., 2003). The oil has a high content (45%) of oleic acid (C-18:1) with respect to other seed oils, and it is also rich (35%) in polyunsaturated linoleic acid (C-18:2) (Charrouf et al., 1999; Khallouki, 2003; Khallouki et al., 2003). Argan oil has a fatty acid composition similar to that of sesame and peanut oil, marketed in Western Europe.

Minor constituents of argan oil

The minor constituents can be divided into two groups. The first group consists of fatty acid derivatives, such as partial glycerides (mono- and diacylglycerols), triterpenes alcohols and phytosterols. The second group includes classes of compounds not related chemically to fatty acids. These are the hydrocarbons, aliphatic alcohols, tocopherols, pigments, phenolics and trace metals. Most of the minor components found in the unsaponifiable fraction of argan oil are phytosterols, triterpene alcohols, tocopherols and xanthophylls.

Triterpene alcohols

The unsaponifiable matter in argan oil contains a proportion of about 20% of triterpene alcohols (Farines in Charrouf et al., 1999). These are a complex group of plant constituents which consist mainly of five condensed cyclohexane rings with 30 carbon atoms. They can be separated from the sterols by chromatography and the few identified in crude argan oil include lupane, ursane and oleanane derivatives which include β-amyrin,

butyrospermol and tirucalol as major triterpenic alcohols and represent 27.3, 18.1 and 27.9 % of the triterpenic fraction, respectively.

Methyl sterols

24-methylene cycloartanol in plants represents the biosynthetic origin of 4-methyl sterols. These sterols are present in small quantities in the triterpenic fractions of the oil. Charrouf et al. (1999) and Khallouki (2003) reported the presence of cycloeucatenol and citrostadienol in argan oil. These methyl sterols do not appear to play any specific biological role and are probably biosynthetic intermediates in the evolution of triterpenic alcohols and sterols.

Sterols

Sterols are tetracyclic compounds with generally 27, 28 or 29 carbon atoms. They constitute a sizeable proportion of the unsaponifiable matter in oil. The total content of sterols in the unsaponifiable fraction of argan oil is about 20%. Farines et al. (1981), Charrouf et al. (1999), Khallouki (2003), Khallouki et al. (2003) report that argan oil contains spinasterol (40%) and its dihydrospinasterol (schottenol, 48%) as major sterols respectively along with δ-7-avenasterol and stigmasta-8,22-diene-3-β-ol in lower concentrations. Spinasterol and schottenol are rarely found in vegetable oils. Spinasterol has been described as the charasteristic phytosterol of the sapotaceae family (Gunasekera et al., 1977). Contrary to the composition of fatty acids, the phytosterol composition is very different from that of sesame and peanut oils in which β-sitoterol dominates.

Vitamin E

Vitamin E is a fat-soluble vitamin, which comprises two major homologous series of compounds (tocochromanols), known as tocopherols and tocotrienols. The tocopherols are structurally characterised by a saturated side chain on the chromatin ring, whereas the tocotrienols possess an unsaturated phytyl side chain. Four homologs of each type are known to exist in nature and they have different degrees of antioxidant and vitamin E activities. Vegetable oils, especially the seed oils, are rich sources of tocopherols. The vitamin E content in crude argan oil ranges between 629 to 660 mg/kg and the major tocopherol (500 mg/kg) is the gamma-analogue (75%) (Khallouki, 2003; Khallouki et al., 2003) correcting mistakes in the literature citing α-tocopherol as the major vitamer (Charrouf et al., 1999).

Carotenoids

Carotenoids are highly unsaturated tetraterpenes, biosynthesised from eight isoprene units. Their more favoured state is the all-*trans*. Carotenoids are divided into two main classes: carotenes which are strictly polyene hydrocarbons, and xanthophylls, which contain oxygen. The oxygen in xanthophylls may be in the form of hydroxy (e.g. zeaxanthin and lutein), keto, epoxy or carboxyl groups. Xanthophylls occur in crude argan oil at a level of 42% of the unsaponifiable fraction (Charrouf et al., 1999).

Squalene

Another point to note is that similar to olive oil Owen et al. (2000), argan oil (compared to other seasoning oils) contains, high contents of squalene (up to 3.2 g/kg) (Khallouki, 2003; Khallouki et al., 2003). Hydrocarbons mainly squalene in vegetable oils are present in quantities generally lower than 0.15%, the exceptions are olive and argan oils, which exceed 0.3%.

Phenolic compounds

Definitive quantification for the first time of some other antioxidants such as vanillic, ferulic and syringic acids along with tyrosol in argan oil has also been achieved (Khallouki, 2003; Khallouki et al., 2003). p-Hydroxybenzoic acid and vanillin are also identified in trace amounts and a number of unidentified compounds with UV spectra similar to phenolics were also detected, and warrant further investigations.

THERMAL STABILITY OF ARGAN OIL

Thermal stability of argan oils compared to sunflower oil with different internal fatty acid compositions, was conducted (Khallouki, 2003) since this oil is typical of those used in the food industry. A range of analytical methods has been adopted to provide information on performance of these oils. Among them, rancidity has been evaluated by means of the measurement of peroxide production (AOAC, 1990). Two forms of argan oil (traditional varieties-aesthetic and food) were the subjects of thorough studies. The physicochemical index, peroxide values (Pv), was compared and good stability (shelf life) of argan oil was observed when oils were thermally stressed in the dark, as partly judged by peroxide value (Pv) curves. In these experiments, argan oil did not exhibit a typical lipid oxidation curve, with the second stage of oxidation at 30 days not reached. The hydroperoxide values in the two varieties showed the same trends and increased with the time of storage of the oils from 2.35 up 140 meq/kg dissolved O_2 after 30 days of incubation (Kallouki, 2003). NMR methodology was also used and good stability of argan oils compared to sunflower oil was observed. Infact even up 63.5°C food argan oil does not absorb oxygen to form hydroperoxides

in sufficient concentration to be detectable by NMR at 250 MHz. The relevant protons at 8-8.5 ppm were totally absent (Khallouki, 2003).

NUTRITIONAL AND BIOLOGICAL FUNCTIONS OF ARGAN OIL AND ITS COMPONENTS

Major components in argan oil and their health effects

The fatty acid composition of argan oil has been the focus of attention in determining its nutritional adequacy in relation to coronary heart disease, (CHD), atherosclerosis, inflammation and cancer risk factors. As indicated earlier, fatty acids in argan oil are balanced by almost 80% unsaturated oleic and linoleic acids and 20% saturated fatty acids. Dietary fatty acids are known to modulate plasma lipids and lipoproteins. This concept has been extensively researched since the early 1950s and evidence has steadily accumulated showing a positive correlation between saturated fat intake and increased levels of plasma total cholesterol (TC) in humans. Oils rich in oleic acid are currently touted to be the healthiest of the edible fats in the human diet (Bartsch et al., 1999). While olive, rapeseed and Canola contain in excess of 60% of their composition as *cis*-oleic acid, argan oil has about 45% of this monounsaturated fatty acid. The question of whether this level of oleic acid in argan is adequate to result in a lipoprotein-cholesterol profile that protects against CHD and cancers must be examined in a series of human trials.

Argan oil is currently under investigation to improve its economic and environmental role. Recent studies (Khallouki, 2003; Khallouki et al., 2003; Drissi et al., 2004) suggest that dietary argan oil, may have a relevant role in disease prevention and its consumption improves plasma lipid profiles, paraoxonase activities, and LDL peroxidation in healthy Moroccan men. The results showed that argan oil consumption protects against atherosclerosis (Cherki et al., 2003).

Minor components in argan oil and their health effects

Some of the minor components in argan oil include the xanthophylls, tocopherols, sterols, squalene, triterpenic alcohols and phenolic antioxidants. Although these minor components account for 1% of the oil constituents, they nevertheless play significant roles in maintaining its stability and nutritional quality (some structures are presented in Figure 2).

Argan vitamin E

Historically, vitamin E activity (one international unit, IU) has been defined as 1 mg of all rac-α-tocopheryl acetate while 1 mg of RRR- α-tocopherol equalled 1.49 IU. In addition, vitamin E activity in foods is expressed as the α-tocopherol equivalent (α-TE) which is the activity of 1 mg of RRR- α-tocopherol. Absorption, transport and metabolism are well described as previously documented (Sokol, 1993). Vitamin E is the principal membrane antioxidant in mammalian cells, although scavenging of reactive oxygen species is not the only mechanism of action of this vitamin, because there are several studies demonstrating activity of tocopherols in cells and tissues that do not directly relate with this. Vitamin E decreases protein kinase C activity, and enhances both phospholipase A_2 and cycloxygenase activity, and modulates several pathways involved in prevention of diseases (Brigelius-Flohe et al., 1999). Most epidemiologic, experimental and clinical studies have evaluated the α-isoform and not the γ-isoform of vitamin E. The crude argan oil contains between 600 and 700 mg/kg tocopherols with the γ form predominating (500 mg/kg) (Khallouki, 2003; Khallouki et al., 2003). Recent epidemiological, experimental and mechanistic evidence suggests that γ-tocopherol may be a more potent cancer chemopreventive agent than α-tocopherol (Gao et al., 2002; Huang et al., 2003). For example It was found that γ-tocopherol is more potent than α-tocopherol in its interaction with reactive nitrogen oxide species (Cooney et al., 1993). In a nested case-control study in Washington County Helzlouer et al., (2000) have examined the effects of α-tocopherol, γ-tocopherol and selenium on incident prostate cancer, and statistically significant protective associations for high levels of selenium and α-tocopherol were found only when γ-tocopherol levels were high. In addition, γ-tocopherol and γ-tocopherol's major metabolite (2,7,8-trimethyl-2-(β-carboxyethyl)-6-dihydroxychroman (γ-CEHC) but not α-tocopherol and its metabolites, show an inhibitory effect of COX-2 activity (Jiang et al., 2000). γ-tocopherol, appears also to beneficially enhance alpha's action (Clement et al., 1997) and has superior ability to inhibit peroxynitrite, a particularly dangerous type of nitrogen-containing free radical (Christens et al., 1997). Moreover, the treatise of the dietary role of γ-tocopherol as a colorectal cancer preventive agent is well reviewed by Campbell et al. (2003). Further work needs to be done to identify the molecular details of these observations. γ-Tocopherol inhibits proliferation of colon cancer cell lines more potently than α-tocopherol and prevents cell cycle progression through reduction in the levels of cyclin D1 and cyclin E and inhibits DNA synthesis more efficiently than α-tocopherol (Gysin et al., 2002).

These abilities of γ-tocopherol may be an important basis for its chemopreventive effects. In addition, vitamin E supplementation can restore various aspects of the immune system that includes an increase of the CD4:CD8 ratio and enhances the ability of T helper cells

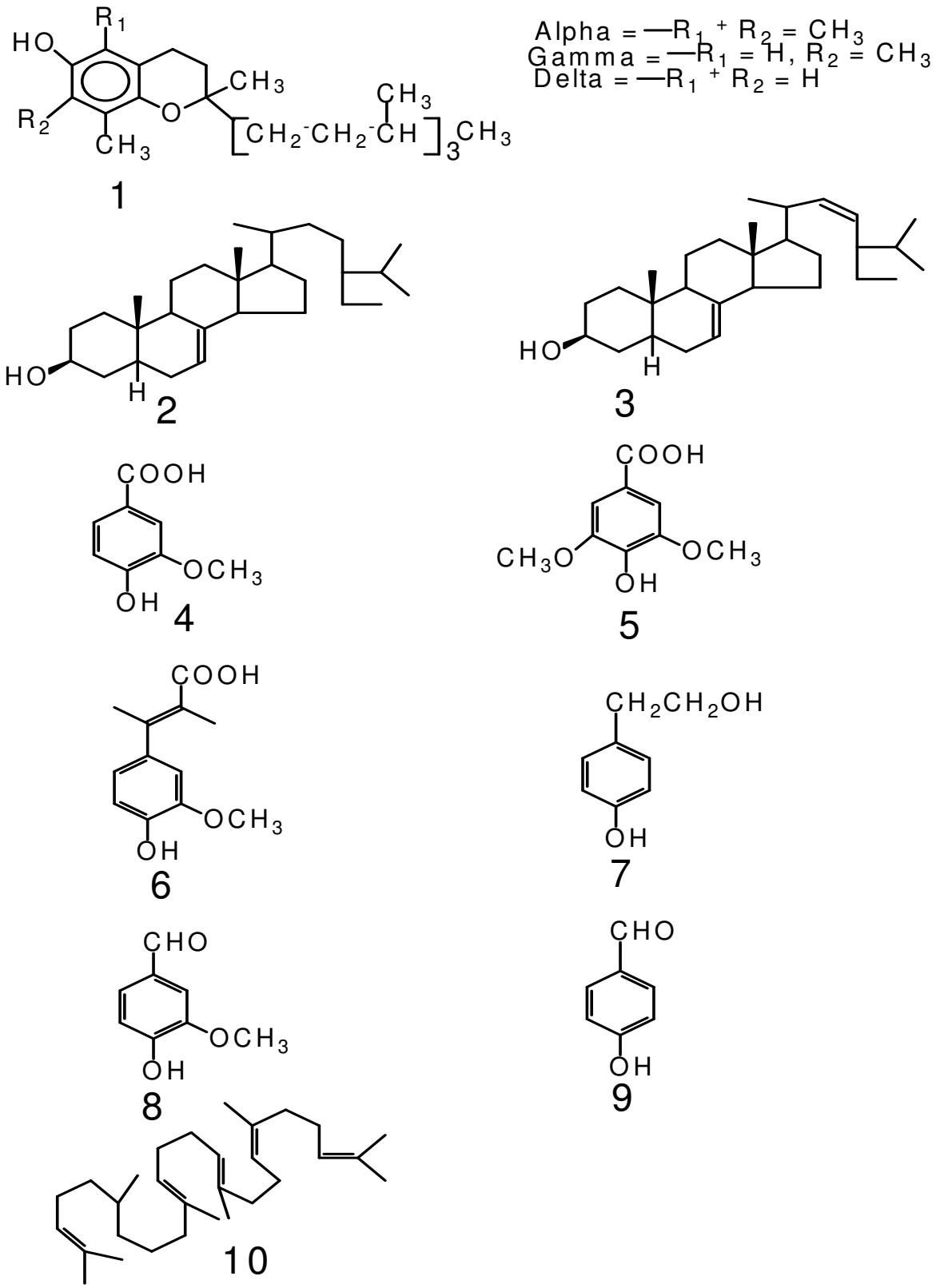

Figure 2. Compounds detected in argan oil. 1. Tocopherols, 2. schottenol, 3. spinsterol, 4. vanillic acid, 5. syringic acid, 6. ferulic acid, 7. tyrosol, 8. vanillin, 9. *p*-hydroxybenzoic acid, and 10.

to produce the cytokines, IL-2 and interferon-γ(Malmberg et al., 2002). Numerous confounding factors influence metabolism and the plasma and tissue levels of γ-tocopherols, which include the lipid content of the diet, inflammation and oxidative stress. The understanding of the exact molecular target of γ-tocopherol's chemopreventive effects would facilitate the design of combination chemoprevention approaches for the prevention of carcinogenesis and more particularly of colorectal cancer. Human chemoprevention trials with γ-tocopherol to determine drug delivery into target tissues, biomarker validation and dose-related studies and effects of combinations of tocopherols with other chemopreventive agents are required. Finally, since most clinical studies have been conducted with supplementations of synthetic vitamin E in high amounts,it remains to be determined if these beneficial effects occur with consumption of γ-tocopherol in amounts naturally present in food such as argan oil.

Argan phytosterols

Squalene is suggested to be protective against skin cancer (Newmark, 1997) and enhances excretion of xenobiotics in rats and mice (Kamimura et al., 1992). In animal studies, its effects are documented to be a reduction in plasma and liver cholesterol levels of mice, modulated by increasing faecal cholesterol excretion (Uchida et al., 1983). Antitumorigenic activity of α-spinasterol has been demonstrated by Villasenor et al. (2000) whereas schottenol exhibits anticarcinogenic and cytotoxic potential (Arisawa et al., 1985).

Argan carotenes

The only carotene detected in argan oil is xanthophyll (Charrouf et al., 1999). Recently Lee et al., (2004) have demonstrated that xanthophyll´s, such as lutein modulates the skin´s response to UVR and may contribute to the defense against some of the deleterious effects of solar radiation, in addition, β-cryptoxanthin and zeaxanthin have been reported to play a role in smoking-related cancer prevention (Ito et al., 1991).

Other secondary metabolites from argan tree

Apart from lipids, only a few studies are devoted to other secondary metabolites of the argan tree. Saponin with protobassic and oeanolic aglycons has been isolated from the methanolic extract of the argan fruit shells and from the aqueous extract of press cake respectively (Charrouf et al., 1992; Alaoui et al., 2002). Saponins which are glycosylated steroids or triterpenes, were tested for their anti-tumor promotion activities (cancer chemopreventive agents) and were shown to be cytotoxic to cancer cells (Fujioka et al., 1996; Hsu et al., 1997; Silva et al., 1997; Konoshima et al., 1998; Gu et al., 2001; Lin et al., 2003; Kim et al., 2004).

CONCLUSION AND PERSPECTIVES

This mini-review is intended to characterize, in depth, precise profiles of chemopreventive substances of the argan tree. This is in the light of the following considerations: (1) *A. spinosa*, because of its wide distribution in Morocco is a source of easily available material in this area (2) information obtained from scientific studies may be of great significance for environmental and human health protection and may also contribute to save this threatened tree.

Future prospects should concern Argan pericarp, leaves, stems and stem barks which may possess biologically and pharmacologically active metabolites that protect the tree from pathogens and parasites and their identifications may shed more light on plant physiology and extend knowledge on argan secondary metabolites. Their identification could also allow the “chemical labelling” of particular cultivars, providing means for their characterization for agronomic purposes.

In our recent pilot studies waste products from the oil production such as the seed and pericarp reveal much higher amounts and diversity (some of which appear to be novel) of polyphenolic and triterpenoid saponins compounds. Therefore characterization and evaluation of these polyphenolic compounds which are promising sources of new and inexpensive antioxidants and their potential chemopreventive and anticancer properties in a range of different *in vitro* bioassays is currently being investigated in our laboratories.

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