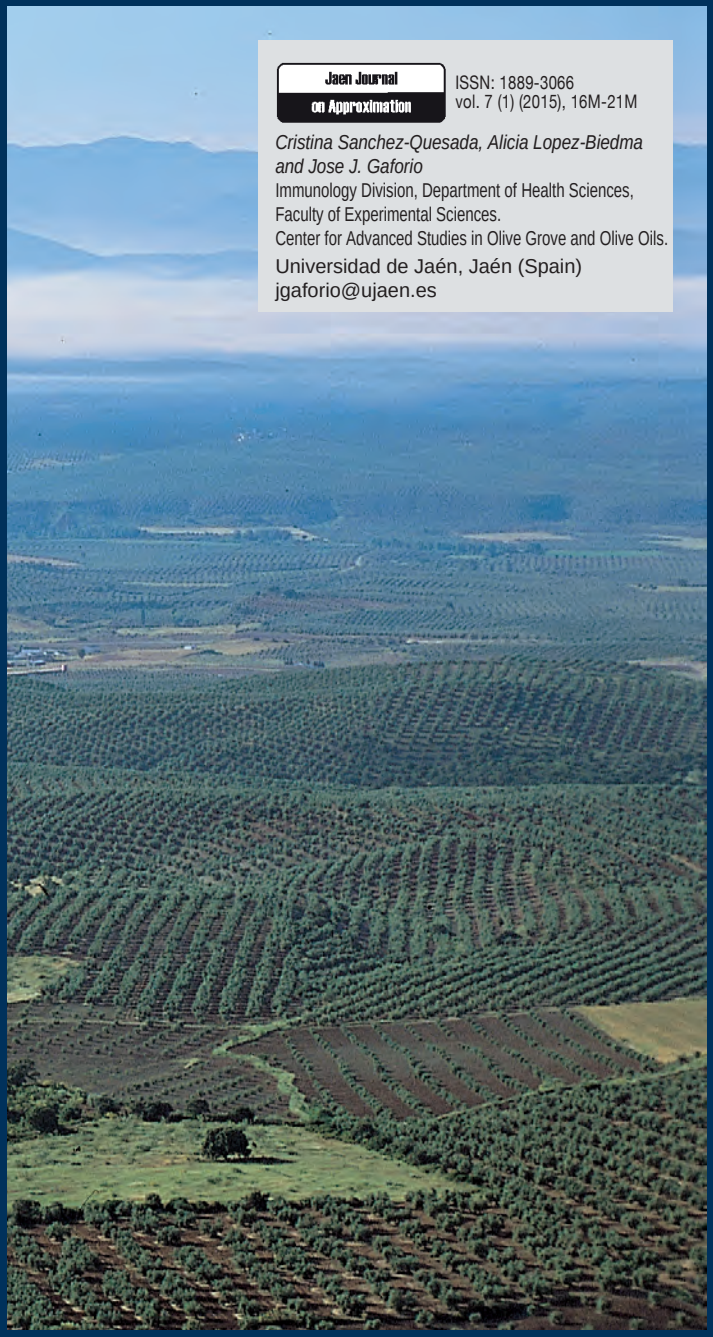
Natural protection against cancer by minor compounds found in virgin olive oil

Jaen Journal on Approximation
ISSN: 1889-3066
vol. 7 (1) (2015), 16M-21M

Cristina Sanchez-Quesada, Alicia Lopez-Biedma and Jose J. Gaforio
Immunology Division, Department of Health Sciences, Faculty of Experimental Sciences.
Center for Advanced Studies in Olive Grove and Olive Oils.
Universidad de Jaén, Jaén (Spain)
jgaforio@ujaen.es



ABSTRACT

Virgin olive oil is the main fat used in the Mediterranean diet. This natural fruit juice contents about 230 different compounds in its minor fraction able to exert beneficial properties in several diseases. Squalene, oleanolic acid, maslinic acid, uvaol and erytrodiol are five of the most representative minor compounds found in virgin olive oil. All of these virgin olive oil compounds have antitumoral effects in different types of cancer, even more they have a natural preventive role in these types of cancer. All the studies remark their potential roles like chemopreventives and even chemotherapeutics in several cases. In conclusion, several beneficial antitumoral properties of virgin olive oil can be explained by its composition, and specifically by the presence of these five compounds in virgin olive oil.

1. Virgin olive oil

The Mediterranean diet has been described to prevent different illness ([45]) and promote human health benefits ([11, 33, 36]).

The most of these benefits could be attributed to Virgin Olive Oil (VOO) which is the main fat source of this kind of diet. Among others, VOO has been described to protect against cardiovascular diseases ([26, 29]), has anti-inflammatory effects ([17]) and promotes apoptosis in different kind of cancers ([12, 2, 28, 27, 34]). It is believed

that these healthy effects are due to minor compounds present in VOO. VOO is composed by triacylglycerides and 1–2% of minor components (about 230 different compounds). It can be divided into two fractions, the unsaponifiable fraction, extracted with solvents after the saponification of the oil, and the saponifiable fraction. In the unsaponifiable fraction of virgin olive oil there is an amount of minor compounds (among 230 different compounds). These minor compounds are being studied for the antitumor effects and preventive actions ([4,5, 32, 44, 3]).

1.1 Minor compounds of virgin olive oil

Among the minor compounds of VOO, there are different groups of natural compounds distinct each other for its chemical structure. They can also be used as effective finger prints (i.e. biomarkers) to evaluate quality and authentication of the olive oils ([1]). Polyphenols, tocopherols, sterols, carotenes, triterpenes and hydrocarbons are some of the groups that we can find in VOO.

There is a major hydrocarbon present at high concentration in shark liver and VOO, squalene (SQ). This compound is an intermediate metabolite in cholesterol metabolism.

SQ, together with the main triterpenes are the most representative compounds of VOO. Oleanolic acid (OA) and maslinic acid (MA) are triterpenic acids present in VOO and uvaol and erytrodiol are triterpenics alcohols. These triterpenes are present in the leaves and skin of olives ([1]).

1.2 Characterization of squalene, oleanolic acid, maslinic acid, uvaol and erytrodiol.

Squalene

Squalene (SQ) is synthetized by squalene synthase, an enzyme that condenses two molecules of farnesyl pyrophosphate with reduction by NADPH to form squalene (Figure 1).

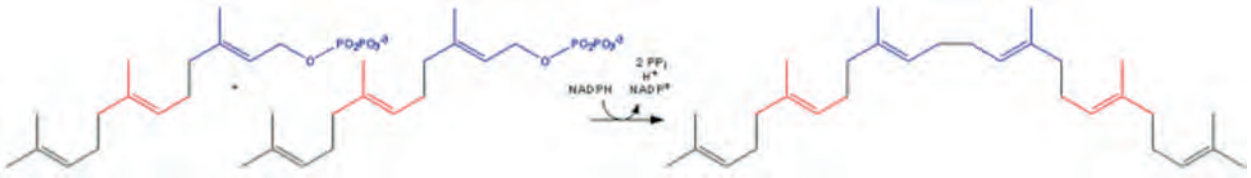


Figure 1. Synthesis of squalene by squalene synthase.

This molecule is a natural 30-carbon organic compound acting as biochemical intermediate in animals (it is the precursor of lanosterol and cholesterol) and plants (being the precursor of stigmasterol). SQ is a hydrocarbon and a triterpene, and is a natural and vital part of the synthesis of all plant and animal sterols, including cholesterol, steroid hormones and vitamin D in the human body ([42]).

In VOO, SQ is the major hydrocarbon (more than 90%), with content ranging from 0,8 to 13 g/kg ([47]).

Oleanolic and maslinic acid

Oleanolic (OA) and maslinic acid (MA) are two hydroxyl pentacyclic triterpene acids differentiated by one vicinal hydroxyl groups at the C-2 position (Figure 2).

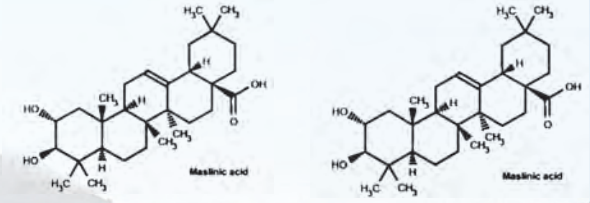


Figure 2. Chemical structure of OA and MA.

These triterpenes are found in olive skin and the leaves of olive tree (Olea Europaea). The Picual variety shows the highest content of this two triterpenic acids with quantities around 110 mg/kg ([1]).

Uvaol and erytrodiol

These triterpenic alcohols are two molecules synthetized in olive tree also, but very little is known about their activity in the human body. However, both possess interesting and useful activities in several diseases. Uvaol (UV) and erytrodiol (ER) differ in a functional group at the C-17 position, which is located in another carbon in uvaol molecule (Figure 3).

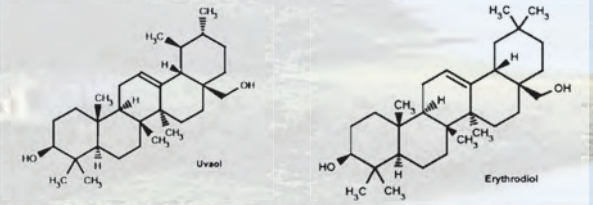


Figure 3. Chemical structure of UV and ER.

Both compounds appear at minor concentrations that triterpenic acids in olives and leaf of the tree ([1]).

Squalene is the precursor of the four triterpenes in the formation of leaves and fruits in the olive tree (Figure 4).

The concentration of all the minor compound fraction will depend on the genetic factors, handing of olive oil and in summary, in the quality of the virgin olive oil ([41]).

2. Bioactivity of minor compounds of virgin olive oil (SQ, OA, MA, UV and ER) in cancer

2.1 Squalene

The major hydrocarbon present in VOO has preventive effects in different illness, like Parkinson disease ([18]) or cardiovascular diseases ([14,37, 3, 6, 15, 16, 24, 30, 37]). But its effects in cancer have been more associated to the preventive that to the antitumoral role. Indeed, some new strategies in cancer are to test squalene derivatives and improve their effectiveness in certain types of cancer ([8, 42, 46]).

SQ is very well-known for its preventive role against several human diseases ([7, 20, 23, 25]) but only a few articles

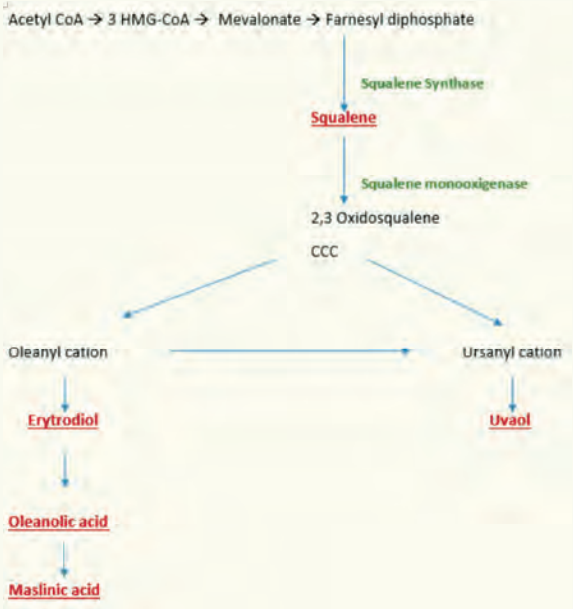


Figure 4. Resume of the biosynthesis taking place in olives and leaf of Olea europaea. "CCC" refers to triple chair form of the molecule.

describe its antitumoral effects ([31, 43]). But the preventive effects are very large, making this compound a good natural option for preventing diverse kinds of cancer diseases ([42]).

SQ has chemopreventive effects in breast cancer in vitro ([47]), on a neuroblastoma model in vitro ([10]), it protects bone marrow progenitors ([9]) and prevents skin, colon and lung cancer ([31, 35, 43]). Moreover, SQ is able to inhibit aberrant hyperproliferation, an event that precedes mammary tumourigenesis in vivo ([19]).

These chemopreventive effects appear to be due to an antioxidant mechanism that this compound promotes inside the cell ([47, 22]), that prevent it from an increase of reactive oxygen species (ROS), that otherwise are responsible of certain kind of carcinogenesis ([21]).

2.2 Oleanolic acid

OA has been studied in different types of cancer cells. And one common effect that oleanolic acid exhibits is its proapoptotic and antiproliferative actions in hepatocellular carcinoma cells, pancreatic carcinoma, non-small-cell lung cancer, lung adenocarcinoma, melanoma cells, breast cancer and colon cancer ([41]). This compound bases its action in the activation cascade of caspases, specifically caspase-3 and caspase-8. OA appears to induce cell cycle arrest in tumoral cells and to control angiogenesis ([41]), a main step in tumor development.

There is no evidence about their preventive role, except for their preventive role in breast human cells in vitro ([40]), but all the scientific works found suggest that this compound is able to have antitumoral effects due to its antioxidant action. While other compounds are not capable of promoting an antioxidant microenvironment for the cell, OA is ([41]).

2.3 Maslinic acid

Scientific studies describe the chemopreventive potential of MA in colorectal cancer in vitro and in vivo and the interesting potential that it has in targeting pro-inflammatory pathways as natural cancer prevention ([41]). But this compound has antimetastatic activity in the development of the different tumors (i.e. prostate cancer cells), activity not described yet in any minor olive oil compound ([34]).

MA also induces apoptosis through caspases pathway in different types of cancer cells as murine melanoma, human colon cancer or salivary gland adenoid cystic carcinoma ([41]).

But like it was mentioned before, MA has natural chempreventive effects through regulation of pro-inflammatory pathways ([39]). MA is able to enhance pro-inflammatory response in human body, to prevent carcinogenesis and even more, MA could intensify inflammatory human response in the early stages of tumor development.

2.4 Uvaol

UV is a triterpenic alcohol not as studied as the triterpenic acids, but with interesting properties. UV inhibits proliferation of several cancer cells of multiple origin like leukemic cells ([13]). A recent work describes the protective role of uvaol in human mammary cells compared to erytrodiol ([38]).

2.5 Erytrodiol

Unless there is no evidence of preventive role of ER in any human cell, ER exerts strong antiproliferative effects in several types of cancer such as skin tumor, breast cancer cells, astrocytoma cells and lymphoma cells ([41]).

Unless ER only differs in the location of a methyl group respect to UV, this distinction confers an antitumoral effect in metastatic breast cancer cells, promoting DNA damage in them ([38]).

3. Conclusion

Numerous scientific evidences support the beneficial properties of squalene, maslinic acid, oleanolic acid, erytrodiol and uvaol. Since all of them are present in virgin olive oils, they could be responsible, at least partially, of health claims attributed to the consumption of these oils. Overall, the available scientific evidence suggests that consumption of virgin olive oils rich in these minor compounds, can contribute to the prevention of certain cancers such as breast cancer or colon cancer.

Bibliography

[1] Allouche, Y. et al. Journal of Agricultural and Food Chemistry 57 (9): 3604-3610; 2009.

[2] Allouche, Y. et al. Journal of Agricultural and Food Chemistry 59 (1): 121-130; 2011.

[3] Bullon, P. et al. Food and Chemical Toxicology 47 (9): 2327-2331; 2009.

[4] Cardeno, A. et al. Food Chemistry 161: 353-360; 2014a.

[5] Cardeno, A.et al. Food & Function. 5 (6): 1270-1277; 2014b.

[6] Chan, P. et al. Journal of Clinical Pharmacology 36 (5): 422-427; 1996.

[7] Cho, S. et al. Clinical and Experimental Dermatology 34 (4): 500-508; 2009.

[8] Cosco, D. et al. International Journal of Nanomedicine 7: 2535-2546.; 2012.

[9] Das, B. et al. Neoplasia 10 (10): 1105-1119; 2008.

[10] Das, B. et al. European Journal of Cancer 39 (17): 2556-2565; 2003.

[11] De Filippis, F. et al. Gut doi: 10.1136/gutjnl-2015-309957; 2015.

[12] Escrich, E. et al. Public Health Nutrition 14 (12A): 2323-2332; 2011.

[13] Es-Saady, D. et al. Mediators of Inflammation 3 (3): 181-184; 1994.

[14] Farvin, K. H. et al. Journal of Medicinal Food 9 (4): 531-536; 2006.

[15] Granados-Principal, S. et al. Molecular Nutrition and Food Research 56 (5): 733-740; 2012.

[16] Guillén, N. et al. Atherosclerosis 197 (1): 72-83; 2008.

[17] Huang, L. et al. European Journal of Pharmacology 672 (1-3): 169-174; 2011.

[18] Kabuto, H. et al. Journal of Oleo Science 62 (1): 21-28; 2013.

[19] Katdare, M. et al. Cancer Letters 111 (1-2): 141-147; 1997.

[20] Kelly, G. S. Alternative Medicine Review 4 (1): 29-36; 1999.

[21] Klaunig, J. E. and L. M. Kamendulis. Annual Review of Pharmacology and Toxicology 44: 239-267; 2004.

[22] Kohno, Y. Biochimica et Biophysica Acta 1256 (1): 52-56; 1995.

[23] Kostyuk, V. et al. PLoS One 7 (8): e44472; 2012.

[24] Kritchevsky, D. et al. Archives of Biochemistry and Biophysics 44 (1): 241; 1953.

[25] Lindholm, J. S. and D. T. Downing. Lipids 15 (12): 1062-1063; 1980.

[26] Lou-Bonafonte, J. M. Current Vascular Pharmacology 10 (4): 392-409; 2012.

[27] Lucio, K. A. et al. PloS One 6 (12): e28596; 2011.

[28] Martin, R. et al. PloS One 4 (6): e5975; 2009.

[29] Martinez-Gonzalez, M. A. et al. Circulation 130 (1): 18-26; 2014.

[30] Motawi, T. et al. Food and Chemical Toxicology 48 (8-9): 2326-2336; 2010.

[31] Murakoshi, M. et al. International Journal of Cancer 52 (6): 950-952; 1992.

[32] Muscoli, C. et al. Journal of Biological Regulators and Homeostatic Agents 28 (1): 105-116; 2014.

[33] Noites, A. et al. Portuguese Journal of Cardiology 34 (11): 655-664; 2015.

[34] Park, S. Y. et al. The British Journal of Nutrition 109 (2): 210-222; 2013.

[35] Rao, C. V. et al. Carcinogenesis 19 (2): 287-290; 1998.

[36] Rotelli, M. T. et al. Surgical Oncology 24 (3): 145-152; 2015.

[37] Sabeena Farvin, K. H. et al. Pharmacological Research 50 (3): 231-236; 2004a.

[38] Sanchez-Quesada, C. et al. Food & Function 6 (1): 248-255; 2015a.

[39] Sanchez-Quesada, C. et al. Evidence-Based Complementary and Alternative Medicine: 654721; 2015b.

[40] Sanchez-Quesada, C. et al. Molecules 20 (8): 13670-13688; 2015c.

[41] Sanchez-Quesada, C. et al. Journal of Agricultural and Food Chemistry 61 (50): 12173-12182; 2013.

[42] Smith, T. J. Expert Opinion on Investigational Drugs 9 (8): 1841-1848; 2000.

[43] Smith, T. J. et al. Carcinogenesis 19 (4): 703-706; 1998.

[44] Stiti, N. et al. In Olives and Olive Oil in Health and Disease Prevention, edited by Victor R. Preedy and Ronald Ross Watson, 211-218; 2010.

[45] Toledo, E. et al. JAMA Internal Medicine 175 (11): 1752-1760; 2015.

[46] Vera, B., A. D. et al. European Journal of Organic Chemistry 2009 (31): 5327-5336; 2009.

[47] Warleta, F. et al. Food and Chemical Toxicology 48 (4): 1092-1100; 2010.