

Health Sciences



U M 6 S S
EDITIONS

Volume 2 | Issue 1

Article 3

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Recommended Citation

Hatimy, Aicha and Kadmiri, Nadia El (2021) "Benefits of Phenolic Compounds Isolated from Olive Oil on Prevention of Cancer," *Health Sciences*: Vol. 2: Iss. 1, Article 3.

Available at: <https://doi.org/10.15342/hs.2020.288>

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REVIEW

Benefits of phenolic compounds isolated from olive oil on prevention of cancer

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ABSTRACT

Traditional Mediterranean diet has long been known to have many health benefits. The diet is associated by the low percentage of certain types of cancers such as colorectal cancer, breast cancer, gastric cancer and prostate cancer. The main source of fats in the Mediterranean diet is olive oil. In fact, the beneficial health effects of olive oil have been attributed to its phenolic compounds like phenolic alcohols, hydroxytyrosol (3,4-dihydroxyphenylethanol) and their secoiridoid derivatives (oleocanthal). Several studies have shown that hydroxytyrosol and oleocanthal are able to inhibit proliferation and induce apoptosis in different tumor cell lines. The aim of this review was to provide an overview of the effect of hydroxytyrosol and –oleocanthal on different types of cancer.

KEYWORDS: Olive Oil; Cancer; Hydroxytyrosol ;(-) Oleocanthal.**Correspondence:** Aicha Hatimy. Faculté Polydisciplinaire de Taroudant, Hay El Mohammadi (Lastah) B.P: 271, 83 000 Taroudant, Morocco. E-mail : aicha.hatimy@edu.uiz.ac.ma**Copyright © 2020 Hatimy A & El Kadmiri N.** This is an open access article distributed under the [Creative Commons Attribution 4.0 International](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**INTRODUCTION**

Nowadays, cancers remain the main health concern in the world.

However, the incidence of cancers is very different around the world, but the Traditional Mediterranean Diet (DM) has the lowest rate of certain types of cancer like colorectal cancer, breast cancer, gastric cancer and cancer. prostate cancer [1]. Cancer has been shown to be preventable through healthy lifestyle choices [2]. Thus, it is better to prevent by consuming a healthy diet than to cure after the onset of the disease. The main source of fat in the Mediterranean diet is olive oil [3], it presents an antioxidant, anti-inflammatory, anti-tumor, anti-aging and anticancer properties due to its chemical composition [4–6]. The chemical composition of olive oil can be classified into two categories, major and minor components. The main components of olive oil are triglycerides, which have a high level of monounsaturated fatty acid. Minor components of olive oil include hydrocarbons, sterols, aliphatic alcohols, tocopherols, pigments, and phenolic compounds [7, 8]. The main phenols in olive oil are phenolic alcohols, secoiridoids, lignans and flavones[9]. Variety of polyphenols may explain olive oil's valuable benefits. The phenolic compounds in olive oil discussed in

this review are hydroxytyrosol and oleocanthal, especially with regard to new knowledge gained in the most recent studies.

SEARCH METHODS

A literature search was carried out through PubMed, google scholar and ScienceDirect databases. Articles examining the cancer prevention benefits of phenolic compounds isolated from olive oil were identified using the following research keywords: "olive oil", "olive oil phenols" "benefits for health", "hydroxytyrosol", "oleocanthal", "anticancer", "secoiridoids". Records were further manually selected according to topic, in particular new finding regarding the role of hydroxytyrosol and oleocanthal in cancer prevention (**Figure1**).

Records that did not meet the eligibility criteria were excluded.

Eligibility criteria:

- Written in the English language.
- Published in peer-reviewed journal.
- Published from 2000 to 2020.
- Papers highlight the effects of Hydroxytyrosol on cancer.

Articles investigate the effects of Oleocanthal on cancer.

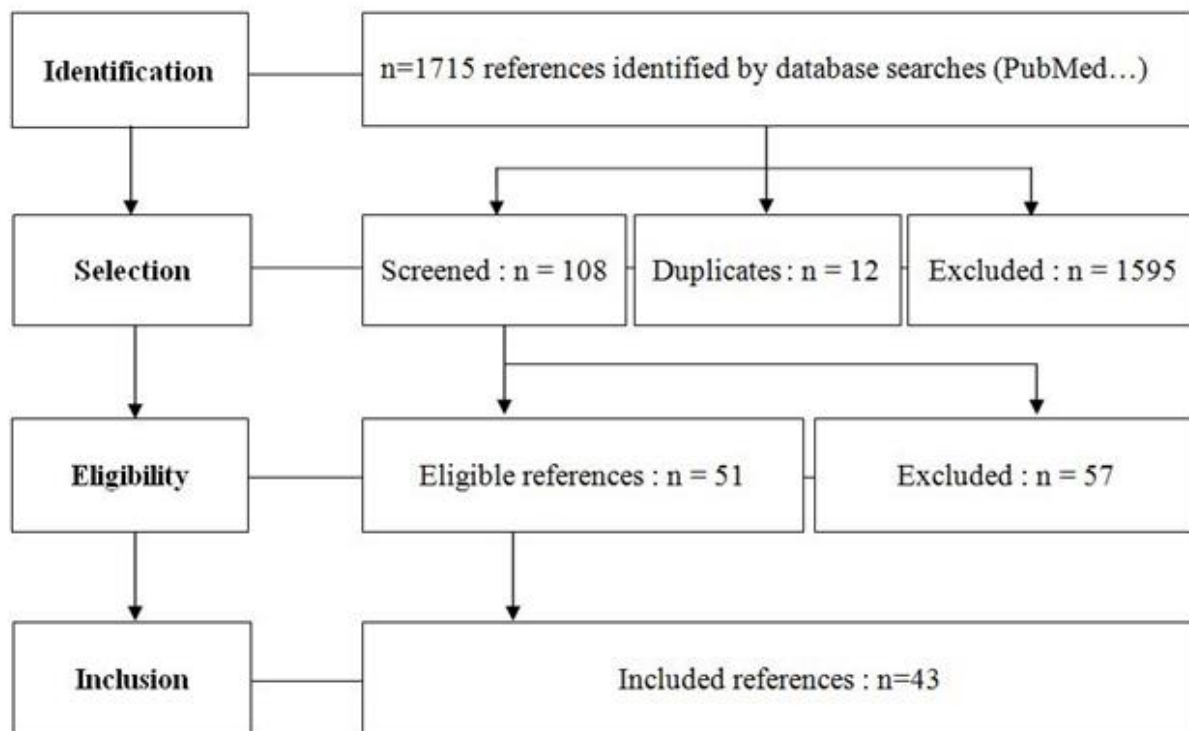


Figure 1: Process of selection of the articles included in the mini-review.

RESULTS

The results are presented in a two-part format: Part one included studies evaluating the effects of hydroxytyrosol on cancer, and part two dealt with studies on the effects of oleochemical on cancer.

Effects of hydroxytyrosol

Out of the thirteen studies, nine studies are included in the first part, it demonstrated the anti-proliferative and apoptotic effects of hydroxytyrosol against types of cancer cells with different types of action. Li et al., and Lopez et al., have revealed the anti-proliferative effects related to cell promotion of apoptosis and cell cycle arrest by suppression mechanism of Akt and NF-κB pathways with p-value<0.05 [10-11]. Concerning the results of Rosignoli et al., they have revealed the anti-proliferative activity by cell cycle arrest in G2 / M phase and also by the ability to suppress the Akt pathways and the nuclear factor kappa B with a p value <0.05 [12]. Likewise, increased intracellular reactive oxygen species ROS were found after incubation with HT with a p-value<0.01[13]. On the other hand, Totoda et al., have demonstrated that the anti-proliferative activity of the different cell lines was inversely correlated with the elimination of H2O2 from the support with a value p <0.05[14].

Effects of oleochemical

The second part included four studies; it has shown that oleochemical has anticancer activity against different types of cancer. Pei et al., correlated the anti-proliferative and apoptotic activities of -Oleochemical with the inhibition of STAT3 by decreasing the JAK1 and JAK2 activity and by stimulating the SHP-1 activity with a p value <0.05 [15]. In addition, the results of Siddique et al., highlighted the anti-proliferative activity of -oleochemical combined with lapatinib (LP). Treatments indicated a synergistic inhibition of cell growth by reducing the activation of focal adhesion kinase (FAK) and paxillin (p-value <0.05) [16]. In contrast, the results of Ayoub et al., showed that -oleochemical has anti-tumor activity. It inhibited 97.06% of tumor growth in athymic orthotopic mice with a p value <0.05 [17]. The latest study by Legendre et al., [18] reported that -oleochemical induced cell death in all cancer cells examined in breast and prostate by inducing lysosomal membrane permeability (PMT) and inhibition of activity sphingomyelin acid (ASM) with a p-value <0.05 [18].

The outcomes of these data discussed in this review are summarized in **Table 1**.

Table 1: A summarized table regrouping studies included in this mini review.

| | Ref. | Cancer type | Treatments | Animal model and control | Main Results | p-value |
|----------------|---|---|---|--------------------------|---|---------|
| Hydroxytyrosol | (Rosignoli, Fuccelli, Vittoria Sepporta, et al. 2016) | Breast (MDA and MCF-7), prostate (LNCap and PC3) and colon (SW480 and HCT116) cancer cell lines | HT (100 μM for 24, 48, 72, 96, 120 and 144 h) | In vitro | HT inhibits the proliferation of all cell lines. | < 0.05 |
| | (López de Las Hazas et al. 2017) | Human colon cancer cells (Caco-2; HT-29) | HT (100–200 μM for 8 and 48 h) | In vitro | HT produces cell cycle arrest and promotes apoptosis. | < 0.05 |

| | | | | | | | | |
|-------------|--------------------------------------|--|---|-----------------------------|---|--|--|--------|
| | (Di Francesco et al. 2015) | Human colon cancer (Caco-2) cells | HT (50 µM for 24 h) | n=18 Sprague-Dawley females | rats | HT up-regulates CB1 tumor suppressor gene via epigenetic mechanisms. | <0.05 | |
| | (Zhao et al. 2014) | Human hepatocellular carcinoma (HepG2, Hep3B, SK-HEP-1 and Huh-7) cells | HT (0–400 µM for 48 and 72 h) | n=30 mice | | HT inhibited proliferation and induced G2/M cell cycle arrest and apoptosis in human HCC cells. | <0.05 | |
| | (Sun, Luo, et Liu 2014) | Human Colon Cancer Cells (DLD1) | HT(50, 100, or 200 µmol L-1) for 24 or 48 h | | In vitro | HT induced apoptosis in Human Colon Cancer Cells Through ROS Generation . | < 0.01 | |
| | (Li et al. 2014) | Human hepatocellular carcinoma (HepG2, Hep3B, SK-HEP-1 and Huh-7) cells | HT (0–400 µM for 48 and 72 h) | n=6 | Male nude mice | HT Inhibited Cholangiocarcinoma Tumor Growth by suppression the activation of Akt and NF-κB pathways | <0.05 | |
| | (Calahorra et al. 2018) | breast cancer cells(MCF-7) | HT (0.1–200 µM) for 16 h | | In vitro | HT modulated the transcription and translation of members of the PGC-1α/ERRα and PGC-1α/Nrf2 pathways | <0.05 | |
| | (Totoda et al. 2017) | Human thyroid carcinoma (TPC-1 and FB-2), papillary and follicular (WRO) cells | HT (65–973 µM for 24 and 48 h) | | In vitro | HT reduced thyroid cancer cells viability by promoting apoptotic cell death via intrinsic pathway. | < 0.05 | |
| | (Giordano et al. 2015) | Human hepatocarcinoma (HepG2) cells under tunicamycin-induced ER stress | HT or hepatic HT-derived metabolites 3-O-HT glucuronide and 4-O-HT glucuronide (10 and 25 µM for 24 h) prior to tunicamycin treatment | | In vitro | Both metabolites glucuronide inhibit ER stress, although they induce a milder change in mRNA expression levels of both CHOP and BiP. | < 0.05 | |
| Oleocanthal | (LeGendre, Breslin, et Foster 2015b) | Human pancreatic cancer cells (BxPC3) Human prostate cancer cells (PC3) Human breast cancer cells (MDA-MB-231) | (-)-Oleocanthal (0.2–20 µM for 4, 24, 48 and 72 h) | | In vitro | Induces cell death in cancer cells by favoring the permeability of lysosomal membranes | < 0.05 | |
| | (Siddique et al. 2019) | Human breast cancer cells (MDA-MB-231, MCF-7 and BT-474) | (-)-Oleocanthal (10–100 ng/mL for 24, 48 and 72 h) | N=20 | Five female nude mice used for each group | (-)-Oleocanthal inhibited the growth of HER2 positive breast cancer cells in vitro and in vivo. | < 0.05 | |
| | (Ayoub et al. 2017) | Human breast cancer cells (BT-474, MCF-7 and T-47D) | (-)-Oleocanthal 5 mg/kg (n=5) 10 mg/kg (n=5) for six weeks | | n=15 | female mice | (-)-oleocanthal inhibited growth of BT-474, MCF-7, and T-47D human breast cancer cells | < 0.05 |
| | (Pei et al. 2016) | Human Hepatocellular Carcinoma (Huh-7, HepG2 and HCCLM3) | (-)-oleocanthal (0–80 µM) for 24–72 h(5–60 µM for 48 h in BT-474 and MCF-7 cells; 10–100 µM for 24 and 48 h in T-47D cells) | | N=24 | Mice (8 mice in each group) | (-)-Oleocanthal Inhibited Growth and Metastasis by Blocking Activation of STAT3 | < 0.05 |

HT : hydroxytyrosol ; HCC : hepatocellular carcinoma ; NF-κB : nuclear factor kappa B ; BC: Breast cancer OC : (-)-Oleocanthal; HER :Human epidermal growth factor receptor; AKT : Protein kinase B;PI3K : Phosphoinositide 3-kinase;MAPK : Mitogen-activated protein kinase;STAT-3 :Signal transducer and activator of transcription 3; CDK-6 : Cyclin-dependent kinase-6;EGF : Epidermal growth factor; HGF Hepatocyte growth factor ;TKIs : Tyrosine kinase inhibitors.

DISCUSSION

Hydroxytyrosol effects on cancer

Hydroxytyrosol (3,4-dihydroxyphenylethanol) is a phenylethyl alcohol, it occurs during the storage of extra virgin olive oil according to the hydrolytic mechanism which forms it from other types of phenolic compounds in the form of secoiridoides [19], [20] and [21]. In recent years, a large number of studies have demonstrated the anti-proliferative and apoptotic effects of hydroxytyrosol against types of cancer cells with different types of action [22]. Additionally, anti-tumor activity has been demonstrated in vitro studies, with significant results in colon (LDD1), cholangiocarcinoma, prostate (LNCaP and PC3) and carcinogenic breast cells (MDA and MCF-7) and hepatocellular carcinomas (SK-HEP-1, Hep3b, Hepg2 and Huh-7).

Li et al., showed that antiproliferative effects were due to cell promotion of apoptosis and cell cycle arrest in several cell types in hepatocellular carcinoma cells (HepG2, Hep3B, SK-HEP-1 and Huh-7) and in cholangiocarcinoma by the Akt and NF- κ B pathway suppression mechanism [10]. Lopez et al., correlated anti-proliferative activity with the ability of hydroxytyrosol to block cell cycles and promote apoptosis [11]. Recording the results of Rosignoli et al., revealed that the anti-proliferative effects of HT were associated with cell cycle arrest in the G₂/M phase and also introduced apoptosis in human hepatocellular carcinoma cells, by the ability to suppress Akt and kappa B channels [12]. Furthermore, Rosignoli et al. [12], correlated anti-proliferative activities with the accumulation of H₂O₂ in the prostate (LNCaP and PC3), breast (MDA and MCF-7), and colon (SW480 and HCT116) cancer cell lines, in other words, the anti-proliferative activity of the different cell lines was inversely correlated with the elimination of H₂O₂ from the medium [12]. Thus, after treatment with HT ROS generated which can play the role of a messenger capable of inhibiting or triggering cell signaling pathways. Finally, Totoda et al., showed that treatment with hydroxytyrosol resulted in a reduction of thyroid cancer cells, by intrinsic, by the death of apoptotic cells [14].

Oleocanthal effect on cancer

-Oleocanthal (OC) is a natural phenolic component of extra-virgin olive oil (EVOO) [23]. It is one of the two enantiomers of oleocanthal, it exhibits antioxidant, anti-inflammatory, anti-tumor activities.

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Current studies demonstrated that oleocanthal had anticancer, as well as anti-proliferative activity against different types of cancer, such as, breast, prostate, pancreatic and hepatocellular cancer. LeGendre et al., showed that OC inhibited cell cycle progression and promotes apoptosis. In this sense, OC induced apoptotic cell death by promoting the permeability of lysosomal membranes. This promotion is done by inhibiting sphingomyelin acid [18]. According to previous findings, Siddique et al., showed that CO combined with lapatinib (LP) treatments in BT-474 and SK-BR-3 breast cancer cell lines indicate synergistic inhibition of cell growth by reducing activation of focal adhesion kinase (FAK) and paxillin [16]. Moreover Ayoub et al., [17] showed that OC has an anti-tumor activity, It inhibited 97.06% of tumor growth in orthotopic athymic mice bearing BT-474. Similarly, LeGendre et al., also reported that OC caused cell death in all cancer cells examined in the breast and prostate by inhibiting their proliferation by inducing lysosomal membrane permeability (PMT) and inhibiting the activity of acid sphingomyelin (ASM) [18].

CONCLUSION

Most recently published studies have confirmed that the phenolic compounds in olive oil have many beneficial health effects; they play a role in cancer prevention. It is therefore better to prevent through a healthy diet than to cure after the onset of the disease.

ACKNOWLEDGMENTS

None.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors](#). Indeed, both authors have actively participated in the redaction, the revision of the manuscript, and provided approval for this final revised version.

COMPETING INTERESTS

The authors declare no competing interests with this case.

FUNDING SOURCES

None.

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