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# Bioinformatics exploration of olive oil: molecular targets and properties of major bioactive constituents

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**Abstract –** Olive oil possesses medicinal properties which include antimicrobial, antioxidant and anti-inflammatory, anti-diabetes, and anti-cardiovascular diseases. Oleic acid is the most abundant (95%) constituent of olive oil and others include linoleic acid, oleuropein, oleanolic acid, maslinic acid, melatonin, and others. The objective of this study is to predict the molecular targets and properties of key bioactive components of olive oil in human. Bioinformatics methods, which involved pharmacokinetics prediction, target prediction and gene network analyses, were used. The results showed that oleic acid has similar targets with linoleic acid, and showed significant probability of binding to several targets such as fatty acid-binding proteins in the adipose, epidermal, liver and muscle as well as alpha, delta and gamma peroxisome proliferator-activated receptors (PPARs). Carbonic anhydrase showed to be the only significant target of tyrosol, while protein-tyrosine phosphatase 1B, and CD81 antigen were targeted by maslinic acid and oleanolic acid. This study has applauded oleic acid, linoleic acid and tyrosol as olive oil bioactive constituents that have several potential pharmacological effects in humans that modulate several enzymes, receptors and transcription factors. The future work will be to investigate the effects of oleic acid on fatty acid-binding proteins and telomerase reverse transcriptase; melatonin on quinone reductase 2; tyrosol on carbonic anhydrase II; maslinic acid and oleanolic acid on protein-tyrosine phosphatase 1B.

**Keywords:** olive oil / bioinformatics / phytochemical / pharmacokinetics / molecular targets / gene network

**Résumé – Exploration bio-informatique de l'huile d'olive : cibles moléculaires et propriétés des principaux constituants bioactifs.** L'huile d'olive possède des propriétés médicinales, notamment antimicrobiennes, anti-oxydantes et des effets bénéfiques sur le diabète, l'inflammation et les maladies cardiovasculaires. L'acide oléique est le constituant le plus abondant (95 %) de l'huile d'olive et les autres comprennent l'acide linoléique, l'oleuropéine, l'acide oléanolique, l'acide maslinique, la mélatonine, et d'autres. L'objectif de cette étude est de prédire les cibles moléculaires et les propriétés des composants bioactifs clés de l'huile d'olive chez l'homme. Des méthodes bioinformatiques impliquant la prédiction de la pharmacocinétique, la prédiction des cibles et l'analyse des réseaux de gènes ont été utilisées. Les résultats ont montré que l'acide oléique possède des cibles similaires à celles de l'acide linoléique, et ont montré une probabilité significative de se lier à plusieurs cibles telles que la protéine de liaison des acides gras dans les tissus adipeux, épidermiques, hépatiques et musculaires ainsi que les récepteurs alpha, delta et gamma activés par les proliférateurs de peroxysomes (PPARs). L'anhydrase carbonique s'est révélée être la seule cible significative du tyrosol, tandis que la protéine-tyrosine phosphatase 1B et l'antigène CD81 étaient ciblés par l'acide maslinique et l'acide oléanolique. Cette étude a mis en avant l'acide oléique, l'acide linoléique et le tyrosol en tant que constituants bioactifs de l'huile d'olive qui posséderaient plusieurs effets pharmacologiques potentiels chez l'homme, qui moduleraient plusieurs enzymes, récepteurs et facteurs de transcription. Les travaux futurs consisteront à étudier les effets de l'acide oléique sur les protéines de liaison aux acides gras et la transcriptase inverse de la télomérase ; la mélatonine sur la quinone réductase 2 ; le tyrosol sur l'anhydrase carbonique II ; l'acide maslinique et l'acide oléanolique sur la protéine-tyrosine phosphatase 1B.

**Mots clés :** huile d'olive / bioinformatique / phytochimie / pharmacocinétique / cibles moléculaires / réseau de gènes

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## 1 Introduction

Olive (*Olea europaea* L.) is an ancient plant that belongs to the family Oleaceae, which contain about 600 species within 30 genera (Iaria *et al.*, 2016). The genus *Olea* L. consists of more than 30 species, which are distributed in Africa, Asia, Europe and Oceania, with only *Olea europaea* subsp. *europaea* var. *europaea* being the cultivated olive (Fogher *et al.*, 2010). Olive oil is produced from the olive plant mainly in the Mediterranean basin which produces 90% of the olive oil consumed worldwide, and it is the principal source of healthy fatty acids, as well as polyphenols and vitamins in minutes (Barbaro *et al.*, 2014; Vasto *et al.*, 2014; Gerber and Hoffman, 2015; Martinez-Gonzalez *et al.*, 2015; Rigacci and Stefani, 2016). Extra virgin olive oil is categorized as a medicinal food because of its nutraceutical benefits and wide range of therapeutic effects such as anti-inflammatory, antioxidant and antimicrobial effect (Cicerale *et al.*, 2012), anti-cardiovascular diseases (Estruch *et al.*, 2006, 2018), diabetes (Salas-Salvado *et al.*, 2011, 2014), neuronal and geriatrics diseases (Khalatbary, 2013; Rodriguez-Morato *et al.*, 2015).

Olive oil contains about 98% fatty acids, principally oleic acid, and 2% minor components of over 230 compounds such as squalene, tocopherols, sterols, and polyphenols (Perez-Jimenez, 2005; Bulotta *et al.*, 2014; Tresserra-Rimbau and Lamuela-Raventos, 2017). Bioactive components of olive oil include oleic acid, tyrosol, hyroxytyrosol, linoleic acid, oleuropein, oleanolic acid, maslinic acid, and melatonin (Segura-Carretero *et al.*, 2010; Fernández-Montesinos *et al.*, 2010; Liu *et al.*, 2010; Bulotta *et al.*, 2014; Tresserra-Rimbau and Lamuela-Raventos, 2017). Extra virgin olive oil contains about 55–83% oleic acid, and 3.5–21% linoleic acid (Cocchi *et al.*, 2009), while virgin olive oil contains about 34.5 $mg.L^{-1}$ tyrosol, 231 $mg.kg^{-1}$ oleanolic acid, and 172 $mg.kg^{-1}$ maslinic acid (Perez-Camino and Cert, 1999; Miró-Casas *et al.*, 2001). Oleic acid is the main constituent of olive oil, which is produced by dehydrogenation from stearic acid by stearoyl-ACP desaturase (SACPD) and then desaturated into linoleic acid by FAD2 (Estruch *et al.*, 2018). Melatonin has been found present in olive oil, specifically in the extra virgin types (Fernández-Montesinos *et al.*, 2010; De la Puerta *et al.*, 2007).

The difference between extra virgin olive oil (EVOO) and virgin olive oil (VOO) is that EVOO has a maximum acidity of 0.8% and may have no defects. VOO can have an acidity up to 2.0% and has a slight change in taste. Pure olive oils are usually refined olive oils, they are obtained from VOO by refined methods and its free acidity is expressed as less than 0.3% of oleic acid. For example, the concentration of maslinic acid increases as the olive-oil quality decreases, from values of 38 $mg.kg^{-1}$ for extra virgin to 227 $mg.kg^{-1}$ for 9.3%-acidity virgin olive, and to 721 $mg.kg^{-1}$ for crude pomace olive oils (Perez-Camino and Cert, 1999). However, the differences in the concentration of bioactive compounds in EVOO and VOO will affect their bioavailability at the sites of action.

The genome sequence and functional annotation of (*Olea europaea* L. subsp. *europaea* var. *europaea cv. "Farga"*) has resulted in 56 349 unique protein coding genes (Cruz *et al.*, 2016), while that of wild olive tree produced over 50 000 protein-coding genes (Unver *et al.*, 2017). Several types of biomarkers such as single nucleotide polymorphisms (SNPs), sequence characterized amplified regions (SCARs) (Fogher *et al.*, 2010), have been used to identify cultivars used in olive oil production (Busconi *et al.*, 2003), and to develop the genetic structure of wild and cultivated olives (Baldoni *et al.*, 2006). Ayed and Rebai (2019) have analyzed 11 Tunisian table olive cultivars based on seven SNP molecular markers (ANTHO3, CALC, FAD2.1, FAD2.3, PAL70, SOD, and SAD.1), to show the possibility of quality authentication and traceability of table olive oil. The functional divergence of oil biosynthesis pathway genes, such as FAD2, SACPD, EAR, and ACPTE, after paralogous event (following duplication), has been responsible for the differential accumulation of oleic and linoleic acids produced in olive when compared with sesame (a closely related oil crop), and the decrease in FAD2 expression and increase in SACPD expression possibly explain the accumulation of exceptionally high levels of oleic acid in olive (Unver *et al.*, 2017).

The impact of dietary olive oil on cancer development have been studied by Zhang *et al.* (2019), where RNA-sequencing technology and comprehensive bioinformatics analyses were used to elucidate the molecular processes regulated by dietary fat. Differentially expressed genes (DEGs) were identified and were functionally analyzed by gene ontology (GO), kyoto enrichment of genes and genomes (KEGG). Then, protein–protein interaction (PPI) network and sub-PPI network analyses were conducted using the STRING database and Cytoscape software. The study suggests that a high olive oil diet aggravates cervical cancer progression *in vivo* and *in vitro* (Zhang *et al.*, 2019). Diet-gene interactions are studied by the concept of nutrigenetics and nutrigenomics, which identify gene variants associated with different responses to nutrients and the effect of nutrients on the metabolic pathways and homeostatic regulation, respectively (Muller and Kersten, 2003; Ordovas and Mooser, 2004). The objective of this study is to predict the molecular targets and properties of key bioactive components of olive oil in human. This work corroborates the targets which have been experimentally discovered, and it also predicts the novel targets which have not been clinically explored, which may be of medical importance in treatment of certain diseases such as cancer, atherosclerosis, nephrotoxicity, inflammation and skin disorder.

## 2 Materials and methods

### 2.1 *In Silico* target prediction

The structure of several bioactive compounds of olive oil as listed in literature (Fernández-Montesinos *et al.*, 2010; Liu *et al.*, 2010; Segura-Carretero *et al.*, 2010; Bulotta *et al.*, 2014; Tresserra-Rimbau and Lamuela-Raventos 2017), were obtained from the PubChem compound database in canonical SMILES (simplified molecular input line entry specification) format. The SMILES of each of these compounds were used for *in silico* prediction of target on the SwissTargetPrediction server, where *Homo sapiens* was selected as target organism (Diana *et al.*, 2019).

**Table 1.** Predicted human protein targets of selected bioactive compounds of olive oil.

| S.No | Target | | | Ligands and percentage (%) probability of binding on target | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Name | Gene ID | UniProt ID | Linoleic acid | Maslinic acid | Melatonin | Oleanolic acid | Oleic acid | Tyrosol |
| 1 | Melatonin receptor 1A | MTNR1A | P48039 | | | 100 | | | |
| 2 | Melatonin receptor 1B | MTNR1B | P49286 | | | 100 | | | |
| 3 | Quinone reductase 2 | NQO2 | P16083 | | | 100 | | | |
| 4 | Serotonin 2b (5-HT2b) receptor | HTR2B | P41595 | | | 40 | | | |
| 5 | Fatty acid binding protein adipocyte | FABP4 | P15090 | 65 | | | | 100 | |
| 6 | Anandamide amidohydrolase | FAAH | O00519 | | | | | 100 | |
| 7 | Peroxisome proliferator-activated receptor gamma | PPARG | P37231 | 75 | | | | 100 | |
| 8 | Peroxisome proliferator-activated receptor alpha | PPARA | Q07869 | 75 | | | | 100 | |
| 9 | Telomerase reverse transcriptase | TERT | O14746 | | | | | 100 | |
| 10 | Fatty acid binding protein epidermal | FABP5 | Q01469 | | | | | 100 | |
| 11 | Peroxisome proliferator-activated receptor delta | PPARD | Q03181 | 75 | | | | 100 | |
| 12 | Free fatty acid receptor 1 | FFAR1 | O14842 | 75 | | | | | |
| 13 | Fatty acid-binding protein, liver | FABP1 | P07148 | | | | | 100 | |
| 14 | Fatty acid binding protein muscle | FABP3 | P05413 | 60 | | | | 60 | |
| 15 | Acyl-CoA desaturase | SCD | O00767 | 30 | | | | 50 | |
| 16 | Cyclooxygenase-1 | PTGS1 | P23219 | 50 | | | | | |
| 17 | Carbonic anhydrase II | CA2 | P00918 | | | | | | 100 |
| 18 | Protein-tyrosine phosphatase 1B | PTPN1 | P18031 | | 70 | | 95 | | |
| 19 | DNA polymerase beta | POLB | P06746 | | 45 | | 70 | | |
| 20 | Aldo-keto reductase family 1 member B10 | AKR1B10 | O60218 | | 55 | | 70 | | |
| 21 | Nuclear receptor ROR-gamma | RORC | P51449 | | 40 | | 60 | | |
| 22 | Receptor-type tyrosine-protein phosphatase F (LAR) | PTPRF | P10586 | | 40 | | 60 | | |
| 23 | T-cell protein-tyrosine phosphatase | PTPN2 | P17706 | | 40 | | 60 | | |
| 24 | 11-beta-hydroxysteroid dehydrogenase 1 | HSD11B1 | P28845 | | 60 | | 60 | | |
| 25 | Low molecular weight phosphotyrosine protein phosphatase | ACP1 | P24666 | | 40 | | 60 | | |
| 26 | Dual specificity phosphatase Cdc25B | CDC25B | P30305 | | 40 | | 55 | | |
| 27 | Phosphodiesterase 4D | PDE4D | Q08499 | | 35 | | 50 | | |
| 28 | CD81 antigen | CD81 | P60033 | | 45 | | 50 | | |
| 29 | Phospholipase A2 group 1B | PLA2G1B | P04054 | | 40 | | 50 | | |

### 2.2 *In Silico* pharmacokinetics

Six active ligands (oleic acid, tyrosol, linoleic acid, oleanolic acid, maslinic acid, and melatonin) were selected based on availability of predicted targets in human with a probability of at least 40% and the SMILES of each of these compounds were used for *in silico* ADME (absorption, distribution, metabolism, and excretion) screening on SwissADME server (Diana *et al.*, 2017). ADME screening was performed at default parameters.

### 2.3 Target gene expression analyses

Twenty-nine genes were obtained from target prediction results for the six bioactive compounds studied which are MTNR1A, MTNR1B, NQO2, HTR2B, FABP5, FABP4, FABP1, FABP3, FAAH, PPARG, PPARA, PPARD, FFAR1, TERT, SCD, PTGS1, PTPN1, POLB, AKR1B10, RORC, PTPRF, PTPN2, HSD11B1, ACP1, CDC25B, PDE4D, CD81, PLA2G1B, CA2 (full name of these genes are listed in the Tab. 1). These genes ID were compiled and used for expression network analyses (transcription factor enrichment analysis and protein-protein interaction network expansion and kinase enrichment analysis), using eXpression2Kinases (X2K) Web server (Clarke *et al.*, 2018), where human was selected as the background organism.

## 3 Results and discussion

The predicted targets and pharmacokinetics of six active constituents of olive oil (oleic acid, tyrosol, linoleic acid, oleanolic acid, maslinic acid, and melatonin) are shown in Tables 1 and 2. The choice was based on the fact that these six compounds have predicted targets genes in human with a probability of at least 40% as shown in Table 1 as well as the amount present in the olive oil. Oleic acid which is the main active constituent of olive oil, has six similar targets with linoleic acid, and showed significant probability of binding to several targets such as fatty acid-binding protein in the adipose, epidermal, liver and muscles as well as peroxisome proliferator-activated receptors (alpha, delta and gamma). It has been reported that PPAR-gamma ligands could inhibit

**Table 2.** Predicted pharmacokinetics parameters of the selected bioactive compounds of olive oil.

| Parameters | Selected bioactive compounds | | | | | |
|---|---|---|---|---|---|---|
| | Linoleic acid | Maslinic acid | Melatonin | Oleanolic acid | Oleic acid | Tyrosol |
| Molecular weight (g/mol) | 280.45 | 472.7 | 232.28 | 456.7 | 282.46 | 138.16 |
| Heavy atoms (HA) | 20 | 34 | 17 | 33 | 20 | 10 |
| Molar refractivity | 89.46 | 137.82 | 67.18 | 136.65 | 89.94 | 39.4 |
| Total polar surface area (Å$^2$) | 37.30 | 77.76 | 54.12 | 57.53 | 37.3 | 40.46 |
| Consensus logP | 5.45 | 5.24 | 1.83 | 6.06 | 5.71 | 1.1 |
| ESOL class | Moderately soluble | Poorly soluble | Soluble | Poorly soluble | Moderately soluble | Very soluble |
| Gastrointestinal absorption | High | High | High | Low | High | High |
| Blood brain barrier (BBB) permeant | Yes | No | Yes | No | No | Yes |
| P-glycoprotein substrate | No | Yes | No | No | No | No |
| Cytochrome P450 inhibitor | CYP1A2, CYP2C9 | – | CYP1A2 | – | CYP1A2, CYP2C9 | – |
| Skin permeation log Kp (cm/s) | −3.05 | −4.56 | −6.59 | −3.77 | −2.6 | −6.84 |
| Lipinski violation | 1 | 1 | 0 | 1 | 1 | 0 |
| Bioavailability score | 0.85 | 0.56 | 0.55 | 0.85 | 0.85 | 0.55 |
| Synthetic accessibility | 3.10 | 6.22 | 1.73 | 6.08 | 3.07 | 1.00 |

tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and IL-1-beta expression in monocytes, iNOS, matrix metalloprotease-9 (MMP-9) and scavenger receptor-A expression in macrophages among others (Krey *et al.*, 1997).

This *in silico* work currently supports the hypothesis that exogenous fatty acids (FAs) enter cell nuclei by binding to FABPs. On getting inside the cell, dietary FAs are reversibly bound to lipid-binding proteins, such as FABPs and acyl-CoA binding proteins, such as Acyl-CoA desaturase (Esteves *et al.*, 2016). Dietary omega-3 polyunsaturated fatty acids (PUFAs) downregulate fatty acid-binding protein-4 in the adipocytes in a sex-dependent fashion and also modulate stearoyl-CoA desaturase activity in an age and sex-specific manner (Balogun and Cheema, 2016; Feltham *et al.*, 2019).

Studies have shown that omega-3 PUFAs or oleic acid could activate the expression of transcription factors such as PPAR (Xu *et al.*, 1999; Brunelleschi *et al.*, 2007) and this may have beneficial effects in human inflammatory bowel disease (Dubuquoy *et al.*, 2006). PPAR has been noted for its indispensable involvement in the neurotrophic effect of oleic acid in neurons (Bento-Abreu *et al.*, 2007). Oleic acid has shown a significantly higher glucosyltransferase (GTF) inhibitory activity and antibacterial activity on *Streptococcus mutans* (Choi *et al.*, 2010). Study has shown that oleate was the most effective down-regulator of FA biosynthesis and cholesterogenesis of various kind of FAs, where it had reduced mRNA abundance, protein level and the activity of both 3-hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase and acetyl-CoA carboxylase (Gnoni *et al.*, 2010).

In this study, carbonic anhydrase showed to be the only significant targets of tyrosol, while protein-tyrosine phosphatase 1B, and CD81 antigen were targeted by maslinic acid and oleanolic acid. Carbonic anhydrase 6, CD209 antigen, and CD44 antigen, have been reported as part of HDL-associated proteins based on the effects of olive oil phenolic compounds (Pedret *et al.*, 2015). Tyrosol is able to inhibit the activation of transcription factors, including NF-κB and STAT-1α, and expression of inducible nitic oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) genes, in cultures of activated macrophages and rat colitis (Moreno, 2003), as well inhibit TNF-α release by LPS-stimulated peripheral blood mononuclear cells isolated from healthy volunteers (Giovannini *et al.*, 2002). Tyrosol also inhibits 5-lipoxygenase, reducing leukotriene B4 and reactive oxygen species (ROS) generation in calcium ionophore-stimulated rat peritoneal leukocytes (De la Puerta *et al.*, 1999). It has been reported that hydroxytyrosol could inhibit human LDL oxidation and platelet aggregation (Morales and Lucas, 2010). Both linoleic and docosahexaenoic acids could cause modulation of gene expression in rat cardiomyocytes (Cheema *et al.*, 2019).

Melatonin receptors are expressed in the tissues of brain (cerebellum and hippocampus), intestine, kidney, and testis. Natural killer (NK) cells, T-lymphocytes, eosinophils, and mast cells possess melatonin receptors (Fatoki *et al.*, 2021). Melatonin could modulate the biological activity and toxicity of tumor necrosis factor- α (TNF-α), increase of interferon- γ production (Fernández-Montesinos *et al.*, 2010). Melatonin administration increases the proliferative response of rat lymphocytes, increases the number of NK cells, stimulates the release of pro-inflammatory cytokines interleukin (IL)-1, enhances phagocytosis and modulates apoptosis (Fatoki *et al.*, 2021).

Maslinic acid (2-α, 3-β-dihydroxyolean-12-en-28-oic acid) is a pentacyclic triterpene abundant in the cuticular lipid layer of olive fruits. Maslinic acid has therapeutic properties related to health and disease, including anti-inflammatory, antioxidant, antiviral, antihypertensive, and antitumor activities (Fernández-Navarro *et al.*, 2010). Oleanolic acid has been recognized as an PPAR-α agonist (Huang *et al.*, 2005). Oleanolic acid and maslinic acid could modulate the activity of DNA polymerase beta (POLB) and protein-tyrosine phosphatase 1B (PTPN1), aldo-keto reductase family 1 member B10 (AKR1B10), nuclear receptor ROR-gamma →(RORC), receptor-type tyrosine-protein phosphatase F (LAR) (PTPRF), 11-beta-hydroxysteroid dehydrogenase 1 (HSD11B1) and others as shown in Table 1.

POLB is involved in the homeostasis of the number of cells, DNA repair, inflammatory response and aging process.

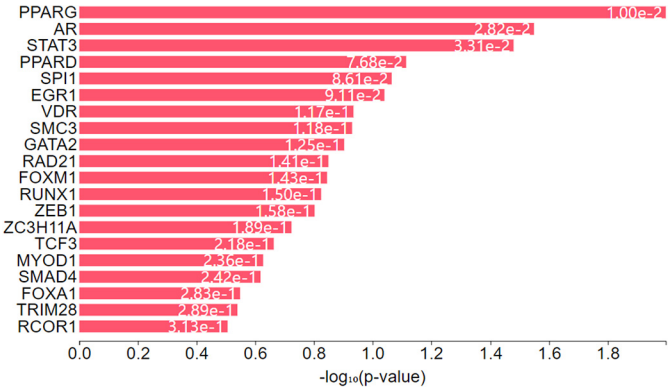


**Fig. 1.** Transcription factor enrichment analysis. The hypergeometric *p*-value indicates better enrichment.

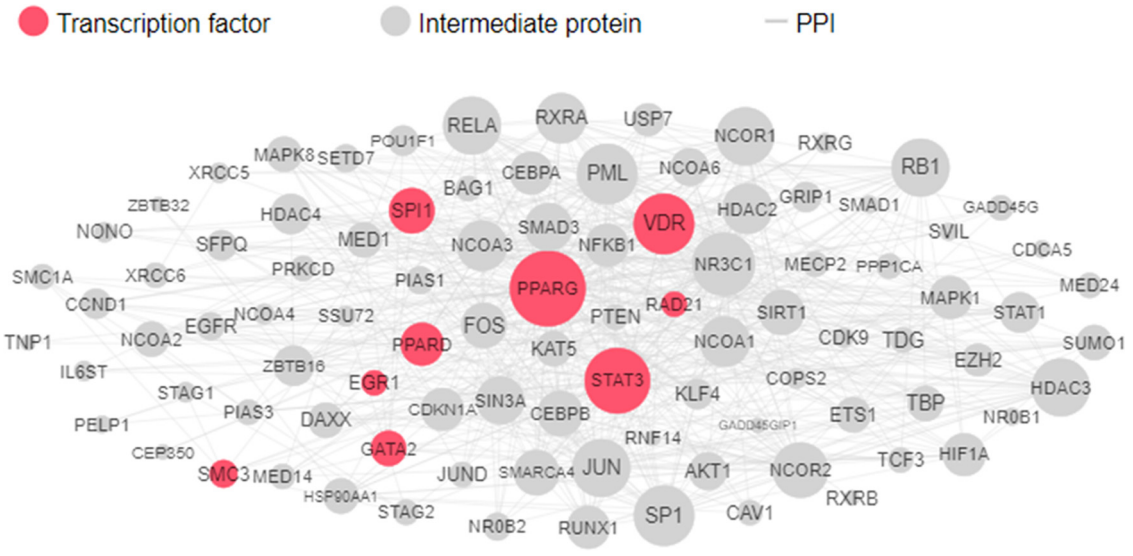


**Fig. 2.** Protein-protein interaction. The red color and its size indicate highly interacted transcription factors.

PTPN1 is a non-receptor type tyrosine-specific phosphatase that dephosphorylates the receptor protein tyrosine kinases (such as INSR, EGFR, CSF1R, PDGFR) and dephosphorylates the non-receptor protein tyrosine kinases (such as JAK1, JAK2, JAK3, Src family kinases, STAT1, STAT3 and STAT6) either in the nucleus or the cytoplasm. It negatively regulates numerous signaling pathways and biological processes like hematopoiesis, inflammatory response, cell proliferation and differentiation, and glucose homeostasis. PTPN1 plays a multifaceted and important role in the development of the immune system. AKR1B10 is highly expressed in the small intestine, colon and adrenal gland, and plays a critical role in detoxifying dietary and lipid-derived unsaturated carbonyls, and their glutathione-conjugates carbonyls. This protein is involved in the retinol metabolism pathway. Thus, maslinic acid and Oleanolic acid could interfere with retinoid metabolic process. Study has shown that maslinic acid and oleanolic acid significantly reduce hyperlipidemia induced by a high-cholesterol diet and lower the expression of the acyl-CoA cholesterol acyltransferase (ACAT) gene (Liu *et al.*, 2010).

As shown in Table 2, oleic acid is moderately soluble, with a high gastrointestinal absorption, serves as an inhibitor for CYP1A2 and CYP2C9, and has a high bioavailability score. This could justify why oleic acid possesses striking therapeutic effects in the intestine, liver and adipose tissues. Although tyrosol has features closely similar ADME properties to oleic acid, it could permeate the blood-brain barrier (BBB) with no action of the cytochromes and not affected by P-glycoprotein. Tyrosol is bioavailable in humans, even from moderate doses of olive oil consumption with substantial variance among women and men (Covàs *et al.*, 2003). The half-life of tyrosol is estimated to be 2–4 h in humans (Covàs *et al.*, 2003). Among the six compounds investigated in this study, tyrosol has the highest skin permeability rate, followed by melatonin. Linoleic acid and melatonin could permeate the BBB and have a high gastrointestinal absorption.

This study shows that peroxisome proliferator-activated receptor gamma (PPARG) has the best hypergeometric score as its transcription factor is influenced by the olive oil, followed by AR, STAT3, PPARD, SPI1, EGR1, VDR, and others (Figs. 1 and 2). The kinases that were impacted by the action of olive oil active constituents include CSNK2A1, MAPKs, CDKs, GSKs, ERKs and HIPK2 (Fig. 3). Moreover, major intermediate proteins include HDAC2, HDAC3,

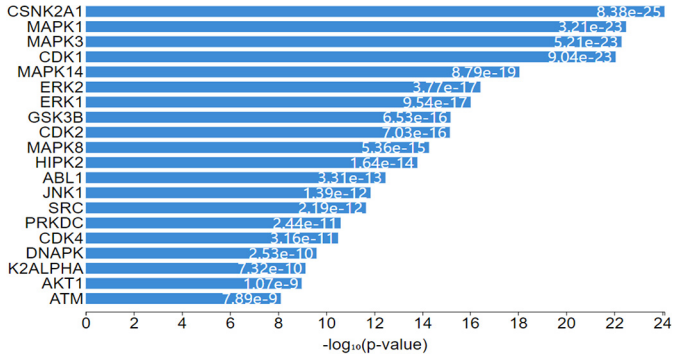


**Fig. 3.** Kinase enrichment analysis. The hypergeometric *p*-value indicates better enrichment.

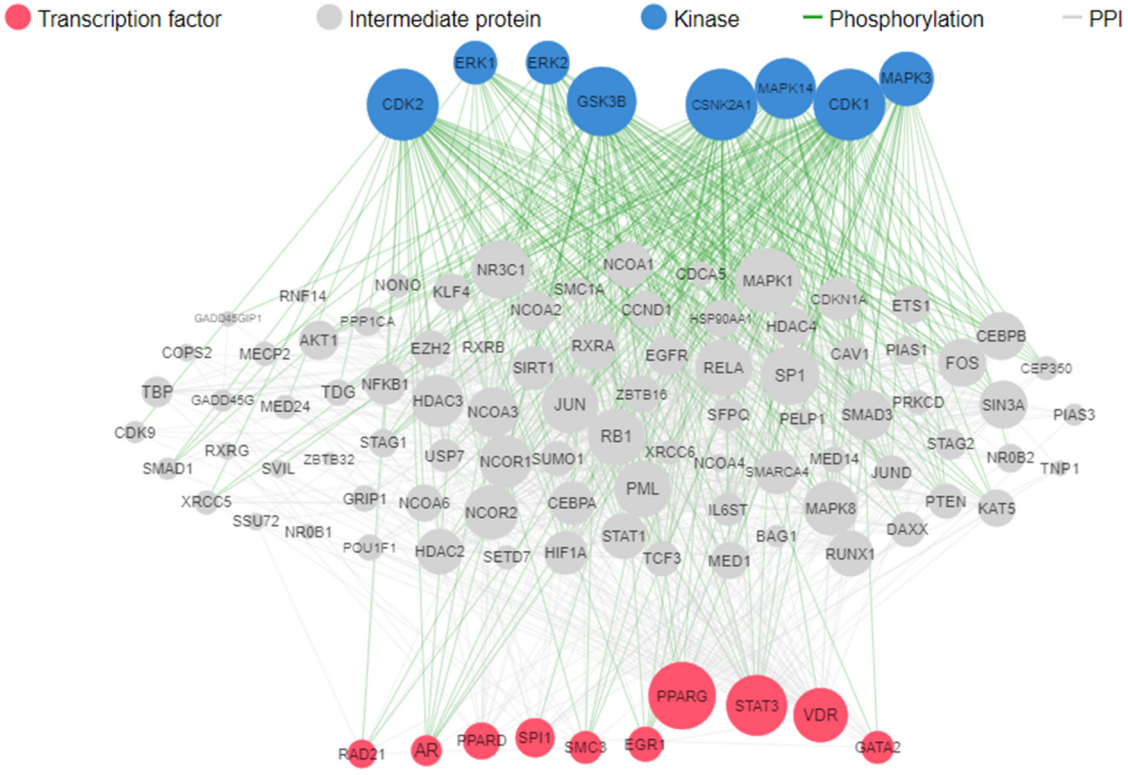


**Fig. 4.** eXpression2Kinases Network. Showing overall interactions of intermediate proteins, kinases and transcription factors.

SMAD2, SMAD3, NCOA3, PML, RELA, JUN, NCOR1 and others (Fig. 4).

Histone deacetylase 3 (HDAC3), HDAC5, LSD1 (a histone demethylase), Atrophin1, and BCL11A have been reported to interact with TLX to regulate the expression of target genes, and has been validated in human Y79 retinoblastoma cells (Wang and Xiong, 2016). Study has shown that oleic acid triggers hippocampal neurogenesis by binding to TLX/NR2E1 and changes it to a transcriptional activator from a transcriptional repressor of cell cycle and neurogenesis genes (Kandel *et al.*, 2020). Thus, through TLX (orphan nuclear hormone receptor), oleic acid could indirectly activate Wnt7a expression, suppresses the expression of p21 *via* a p53-dependent mechanism, promotes EGFR signaling in brain cells, and modulates the mitogen-activated protein kinase (MAPK) pathways (Wang and Xiong, 2016) and enhances STAT1 function (Beiting *et al.*, 2015). A bioinformatics study conducted to predict peroxisome proliferator-activated receptors (PPARs) gene targets on a genome-wide basis, has shown that PPARs could directly regulate some genes such as chromatin remodeling, DNA damage response, Wnt, and mitogen-activated protein kinase (MAPK) (Lemay and Hwang, 2006). FAs and eicosanoids can regulate gene transcription through PPARs (Kliewer *et al.*, 1997; Kersten *et al.*, 2000).

## 4 Conclusion

Knowledge of bioinformatics as it is being applied in lipidomics of a given organism, has not been fully applied to the study of lipids as therapeutics, in order to predict the

acclaimed medicinal properties. This study has applauded oleic acid, linoleic acid and tyrosol as olive oil bioactive constituents that have several potential pharmacological effects in human by modulating several enzymes, receptors and transcription factors. Moreover, these molecular effects of olive oil indicate its medicinal importance in the treatment of oxidative stress, inflammation, cardiovascular diseases, obesity, diabetes, and age-related diseases. Furthermore, chemical biology and *in silico* simulation of pharmacological potential of oleic acid (such as molecular docking and dynamics, drug-drug interaction) will yield significant insights to the presently unexplored molecular mechanisms of action to explain the therapeutic effect of olive oil. The future work will be to investigate the effects of oleic acid on fatty acid-binding proteins and telomerase reverse transcriptase; melatonin on quinone reductase 2; tyrosol on carbonic anhydrase II; maslinic acid and oleanolic acid on protein-tyrosine phosphatase 1B.

*Conflicts of interest*. The authors declare no conflicts of interest.

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