Dr Marc Maresca

Aix Marseille University (France)

Jointly elaborated by: University of Novi Sad (Serbia)

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Mediterranean Food Industry By-Products and Wastes as a Source of Phytochemicals with Health Effects.

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Agri-food Waste Management for Sustainable bio-economy through Higher Education curricula and upskilling

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Goals

AGRIMA aims to foster universities' **capacity building** for the **green transition** through **innovative practices and higher education curricula updating in agri-food waste management** for the **circular bioeconomy**.

AGRIMA addresses:

1. **Advancing pedagogical methods** for industrial agri-food waste valorisation **based on business-academia synergies**.
2. **Integrating citizen science** in bio-economy-enhanced waste valorisation as a means of **civic engagement and environmental advocacy**.

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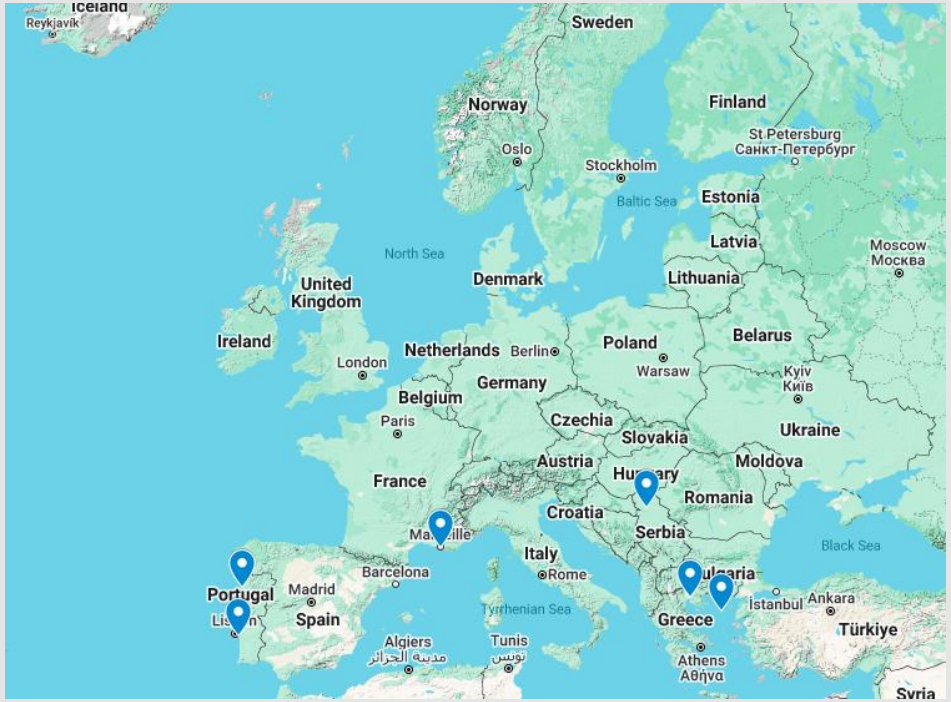

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Mediterranean Food Industry By-Products and Wastes as a Source of Phytochemicals with Health Effects.

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What is called the « Mediterranean diet » ?

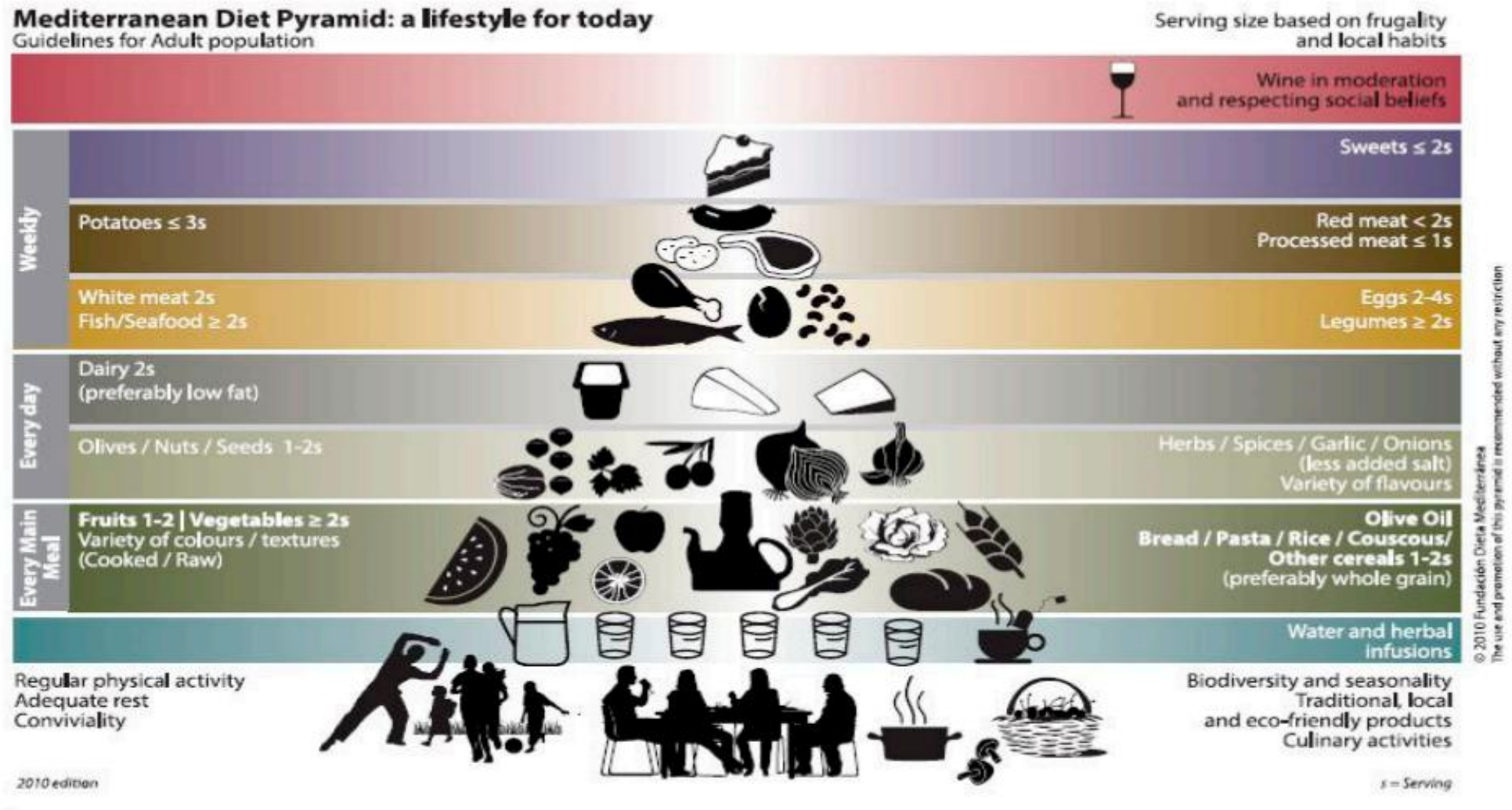

Figure 1. Mediterranean diet pyramid. Source: Fundacion Dieta Mediterrànea (from Mentella *et al., Nutrients*, 2019, 11, 2059; doi:10.3390/nu11092059).

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Mediterranean diet : good for you and for the Earth (but also for your wallet !)

Figure 2. Double Pyramid proposed by Barilla Centre for Food and Nutrition—Source: Barilla Center For Food and Nutrition (https://www.barillacfn.com/en/dissemination/double_pyramid/) (from Mentella *et al., Nutrients*, 2019, 11, 2059; doi:10.3390/nu11092059).

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What are observed health effects of the Mediterranean diet ?

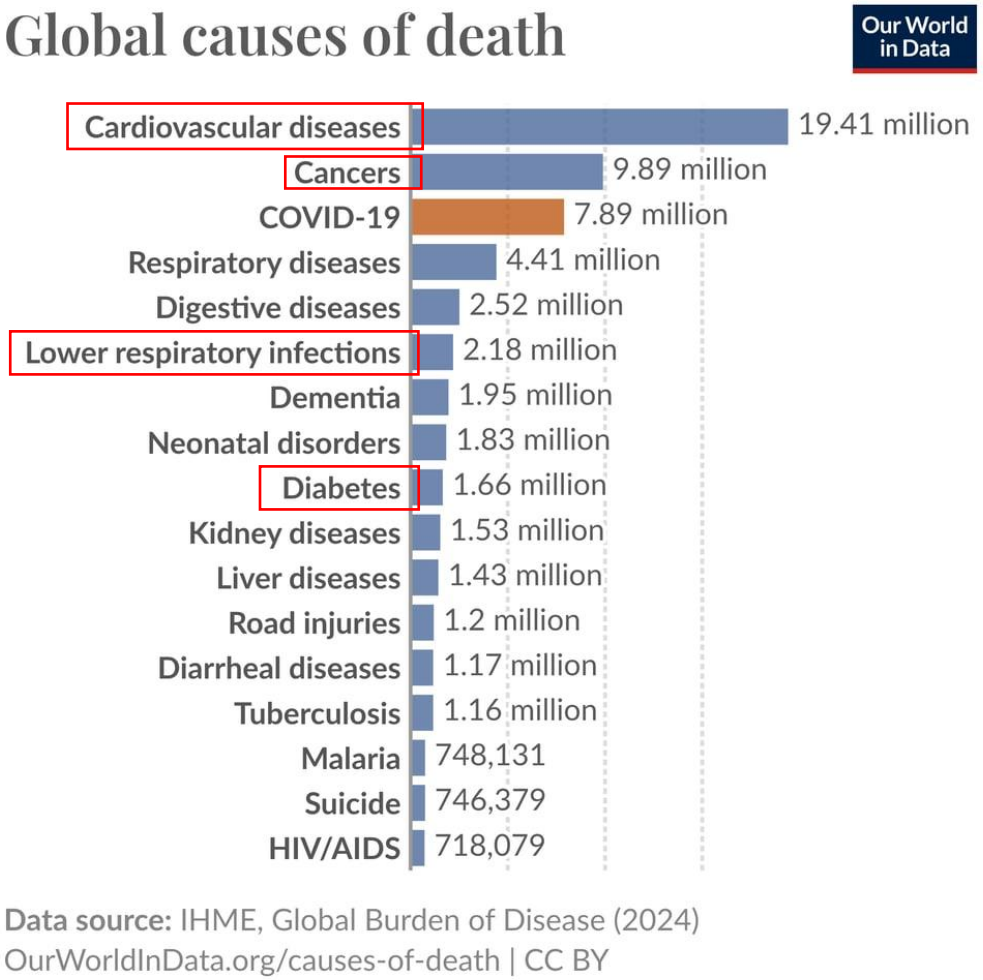

Figure 3. Left image: Characteristics of the Mediterranean diet and associated health benefits (from Agaj *et al., Molecules,* 2022, 27, 8655. https://doi.org/10.3390/molecules27248655). **Right image:** Annual number of deaths by cause. The Mediterranean diet may help preventing deaths related to cardiovascular diseases, diabetes, cancers, or infections.

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Focus on the anti-cancer effect of the Mediterranean diet (suspected or proved)

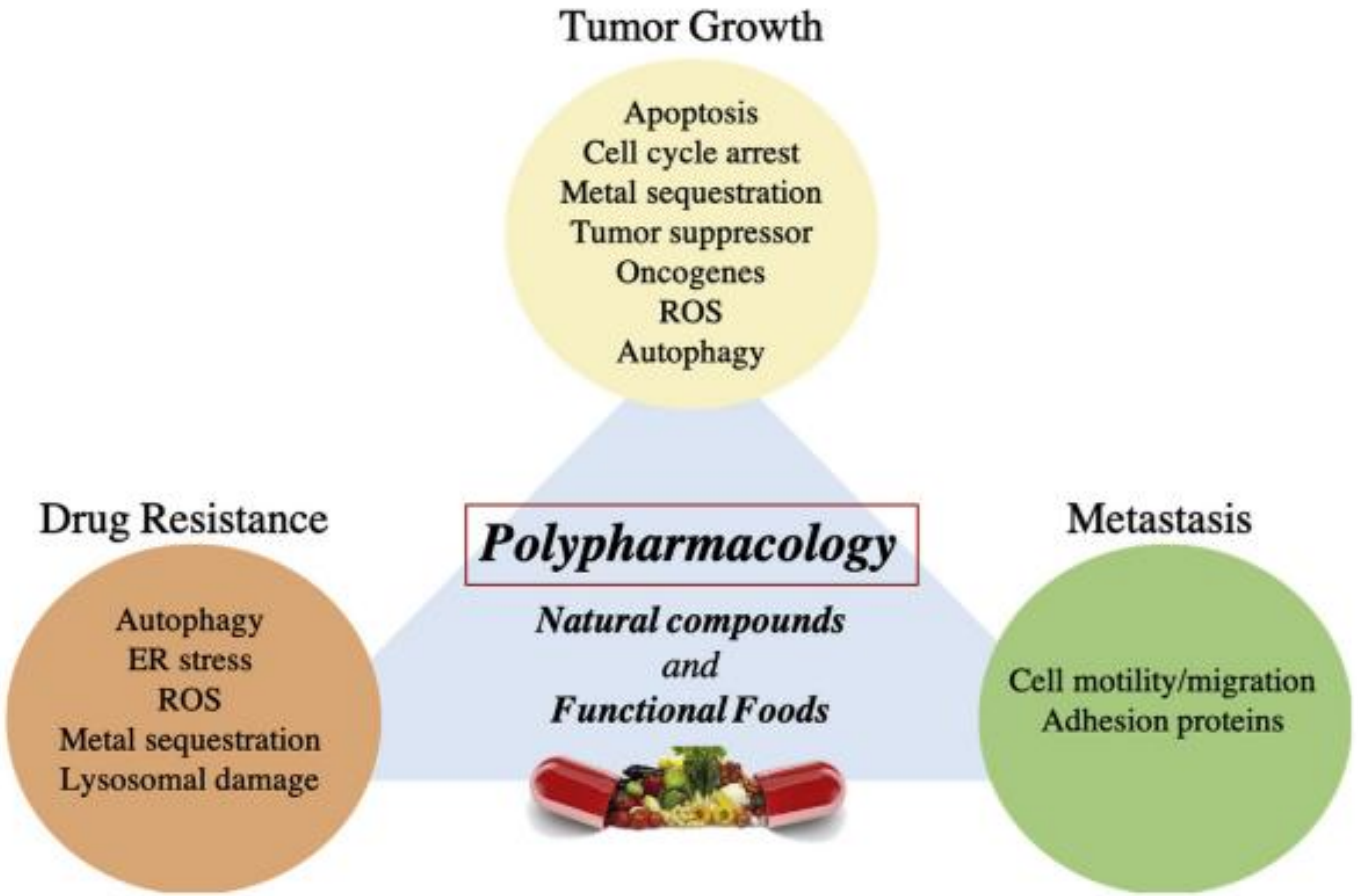

Figure 4. The polypharmacology effects of natural compounds and functional foods in the main cancer pathways (from Maruca *et al., European Journal of Medicinal Chemistry*, 2019, https://doi.org/10.1016/j.ejmech.2019.111579 0223-5234).

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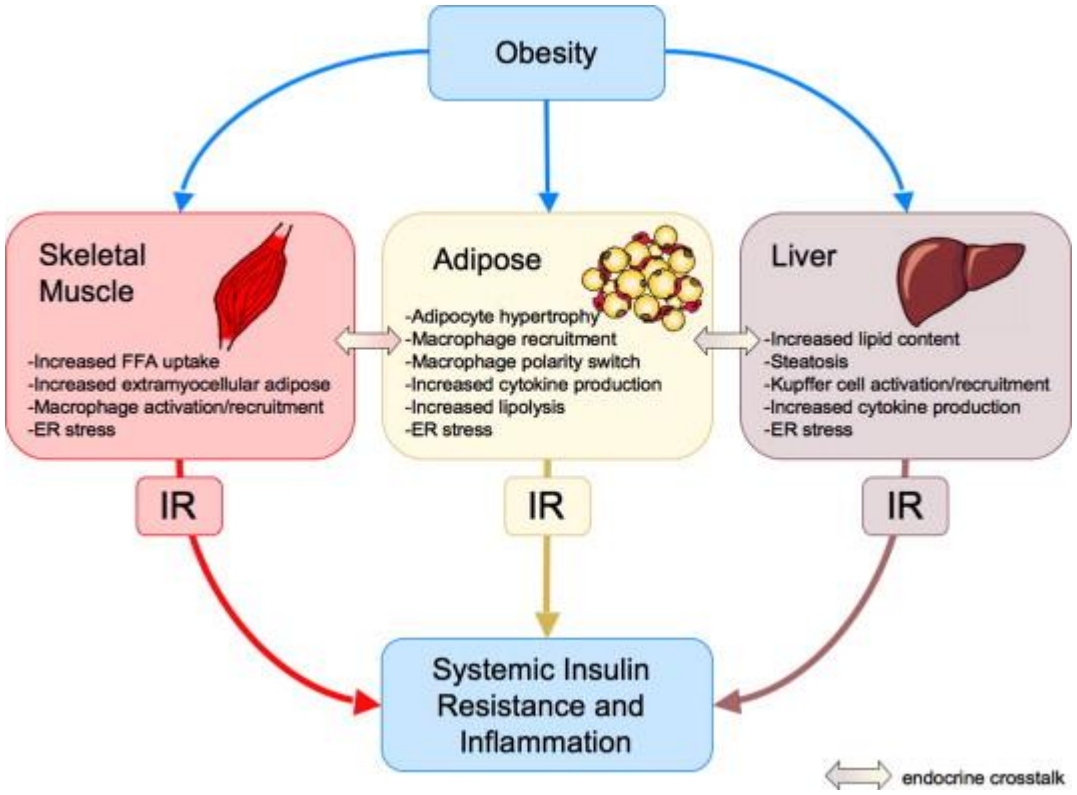

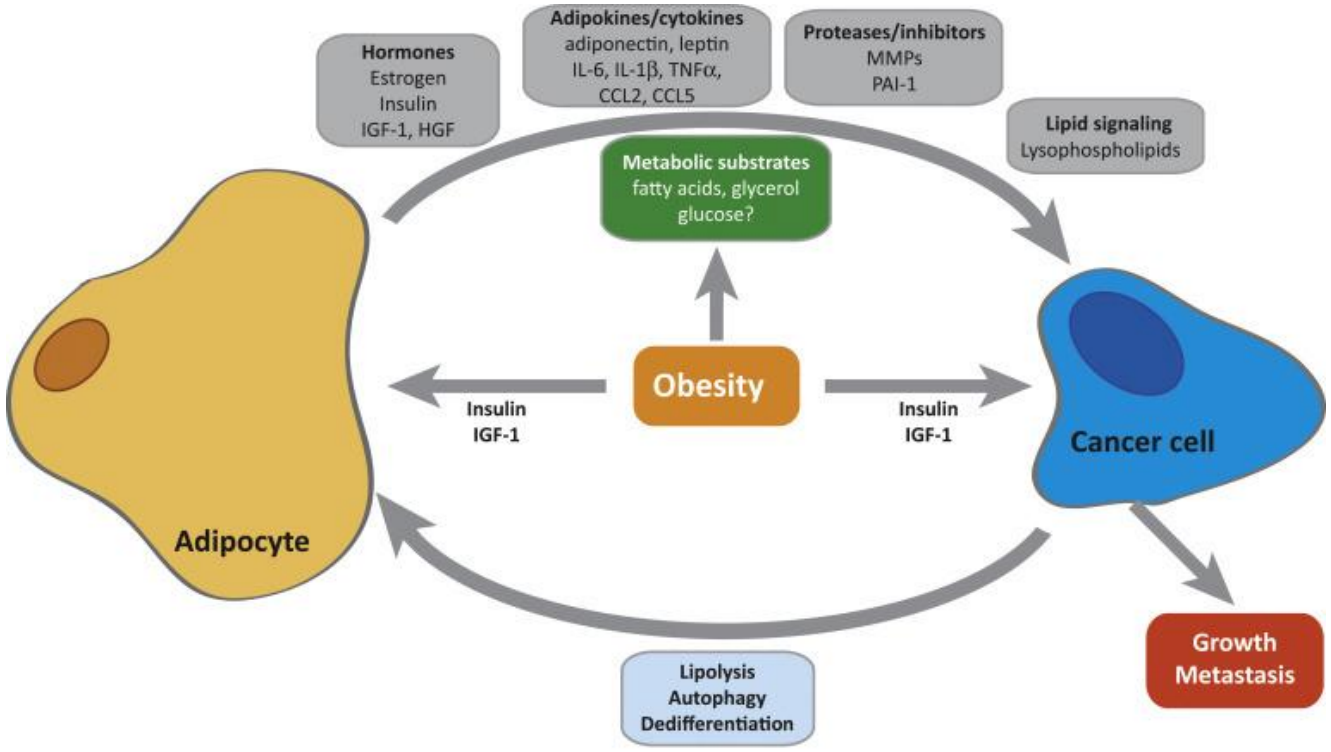

Figure 5. The link between « bad food » (rich in saturated fatty acids and sugar) and diseases. Diet rich in saturated fatty acids and sugar causes obesity which leads to chronic inflammation in adipocytes and liver. This “visceral” chronic inflammation leads to type-2-diabetes (insulin resistance) and higher risk of cancer (due to oncogenic mutations caused by ROS).

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Focus on the anti-cancer effect of the Mediterranean diet (suspected or proved)

Ajouter des images bien / pas bien

Typical Foods	Elements	Function	Cancer
Fruits & Vegetables	Antioxidants and micronutrients (carotenoids, vitamin C, vitamin E, selenium, dietary fiber, dithiolthiones, glucosinates, polyphenols, protease inhibitors, allium compounds, plant sterols, and limonene)	Anti-tumorigenic effect	Less risk of: -Epithelial cancer -Digestive tract cancer -Breast cancer -Female genital tract cancer -Urinary tract cancer
Fish	Long-chain omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid	Reducing tumor cell growth Modulation of transcription factor activity and signal transduction Alteration of oestrogen metabolism	Less risk of: -Liver cancer -Colorectal cancer
	Heterocyclic amines and polycyclic aromatic hydrocarbons may be formed when fish is cooked on a grill or barbecue	Production of mutagenic chemicals	High risk of stomach cance
Olive oil	Polyphenols (oleuropein and hydroxytyrosol)	Antioxidant activity, anti-inflammatory and anti-mutagenic effects	Less risk of: -breast cancer -ovarian cancer -upper aero-digestive tract cancer -colorectal cancer
	Oleic acid, poly unsaturated fatty acids (PUFA), low n-6 PUFA/n-3 PUFA ratio	Chemoprotective effect	
Meat	Heterocyclic amines and polycyclic aromatic hydrocarbons formed when meat is cooked at high temperatures	Carcinogens	High risk of: -colorectal cancer -nasopharynx cancer -ung cancer -pancreatic cancer -bladder cancer -esophagus cancer (squamous cell carcinoma) -stomach (no-cardia) cancer
	Haem iron, present in high level	Promotion of tumorigenesis by stimulating the endogenous formation of carcinogenic N-nitroso compounds	
	High-temperature cooking of red and processed meats may enhance production of advanced glycation endproducts (AGEs).	Produce several cancer-promoting effects	High risk of pancreatic canc
	Consumption of meat may lead to insulin resistance and hyperinsulinemia, promoting growth of cancer cells	Promoting growth of cancer cells	
Whole grains	Provide various nutrients: vitamin E, selenium, copper, zinc and bioactive non-nutrient compounds (lignans, phytoestrogens, and phenolic compounds), and dietary fiber	Anti-carcinogenic properties, as anti-oxidative activity Reduce insulin resistance	Less risk of: -colorectum cancer -upper aero-digestive tract -stomach cancer -breast cancer -ovarian cancer -kidney cancer
	Aflatoxin (mycotoxin produced by molds of the Aspergillus species)	High mutation load in TP3	High risk of liver cancer
Dairy Products	Calcium, lactic acid-producing bacteria, vitamin D, linoleic acids, lactoferrin,	Inhibit tumor development	Less risk of: -breast cancer (pre-menopausal and post-menopausal women) -colorectal cancer
	High level of calcium	Downregulating the formation of the biologically active form of vitamin D → increasing cellular proliferation	Higher risk of prostate cancer
Red Wine	Phytoalexin presents in grape skin	Antioxidant and cancer chemo preventive agent → inhibiting tumor initiation, promotion and progression	Controversial results about impact
	Resveratrol and quercetin	Modulating cell cycle-regulating proteins Inducing apoptosis in multiple carcinoma cell lines Anti-inflammatory, growth → inhibiting activity and immunomodulation properties	

Information source: World Cancer Research Fund and Grosso et al. (2013).

Table 1. Example of elements linked with Mediterranean diet, effect of elements on cancer and cancer risk for each element (from Mentella *et al., Nutrients*, 2019, 11, 2059; doi:10.3390/nu11092059).

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How does it work ? What are i) the molecules involved and ii) their mechanisms of action ?

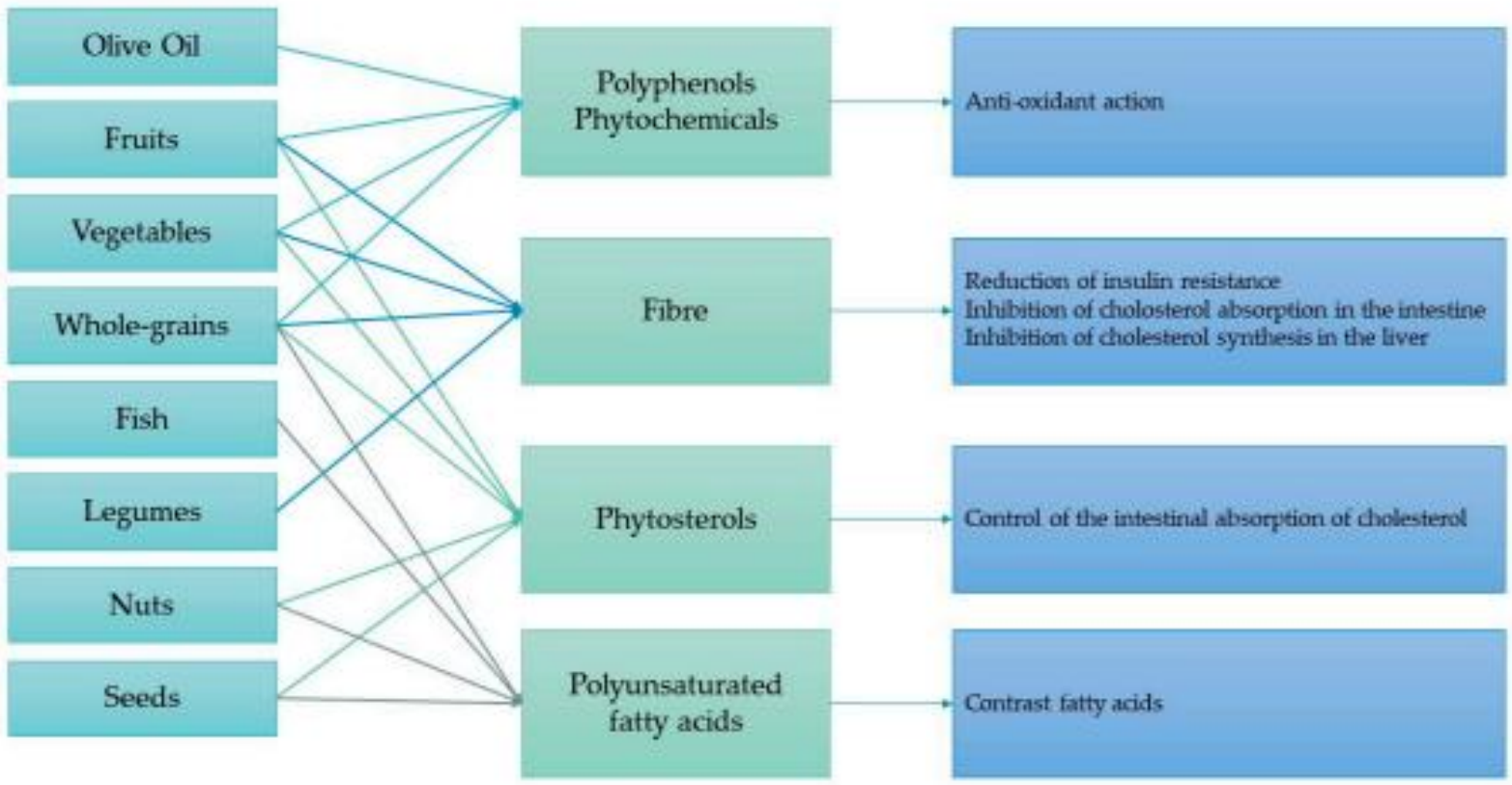

Figure 6. Mechanism between Mediterranean diet components and beneficial effects (from Mentella *et al., Nutrients*, 2019, 11, 2059; doi:10.3390/nu11092059).

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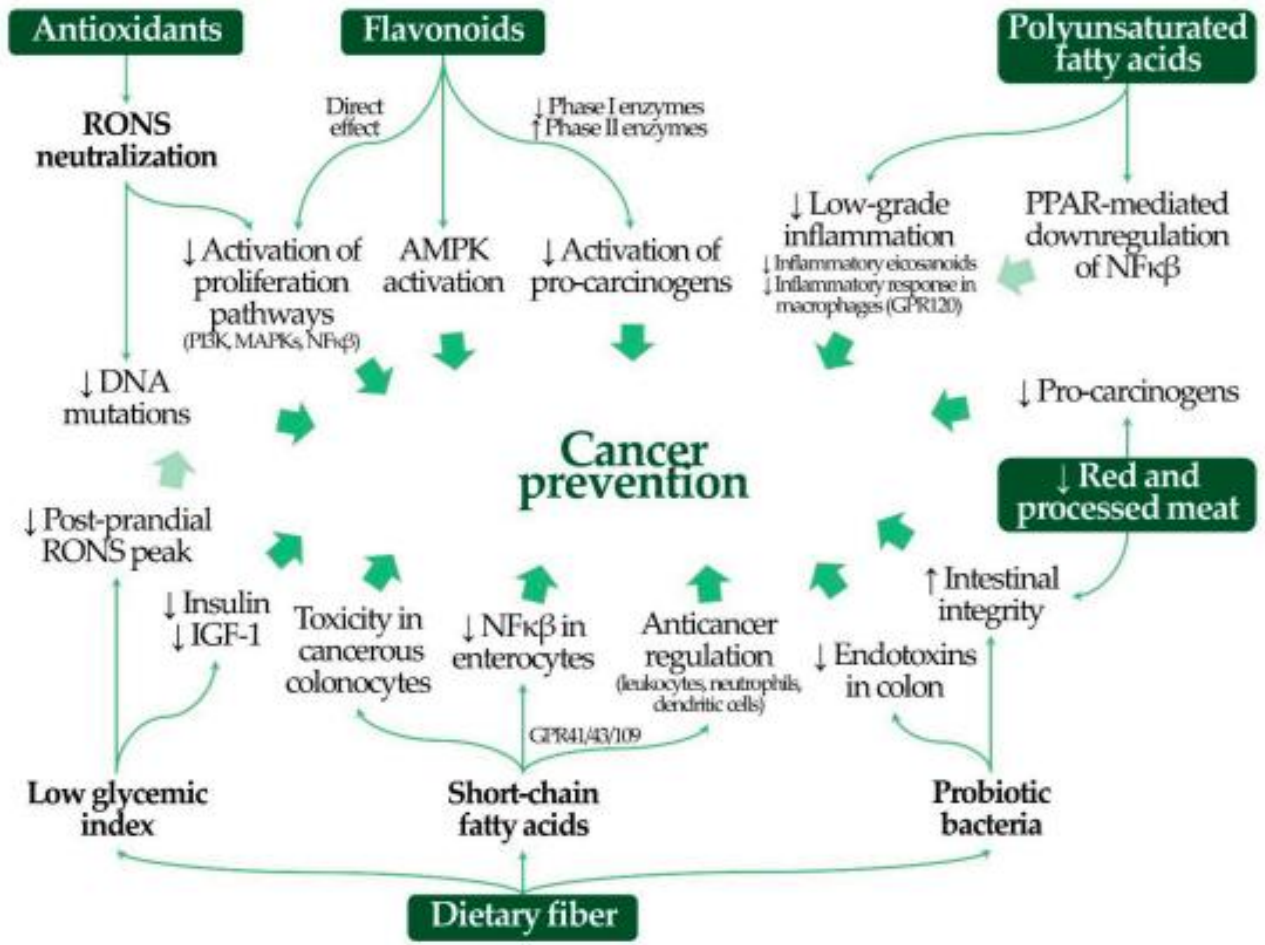

Figure 7. Molecular mechanisms of Mediterranean diet bioactive dietary components on cancer prevention. AMPK: AMP-mediated protein kinase; IGF-1: insulin-like growth factor-1; MAPKs: mitogen-activated protein kinases; NFκβ: nuclear factor kappa beta; PI3K: phosphoinositol-3-kinase; PPAR: peroxisome proliferator-activated receptor; RONS: reactive species of oxygen and nitrogen (from Hernáez and Estruch, *Nutrients,* 2019, 11, 2155; doi:10.3390/nu11092155).

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Knowing the beneficial health effects of the Mediterranean diet, what about Mediterranean Food Industry By-Products and wastes ? Can they have beneficial health effects ?

- Million tons of agricultural by-product waste are generated worldwide, including from the Mediterranean Food Industry
- These by-products and wastes consist of non-edible parts such as peel, stem, seeds, and pulp, among others
- These non-edible parts may have a similar content of bioactives compounds as the edible parts that are consumed
- Are these by-products / wastes, cheap and easily accessible in large amounts, a potential source of molecules with health effects that can be used as pharmaceuticals, nutraceuticals, and/or cosmetics ?
- Some examples of by-products and wastes from
  - Olives and Olive oil
  - Tomato
  - Tuna
  - Pomegranate

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Example 1: By-products and wastes from Olives and Olive oil

Production of Olive Oil Mill Waste Water (OMWW) has been estimated at around 20 million m^3 (equivalent to 20 million tons) per year worldwide. Can OMWW be a source of active compounds ?

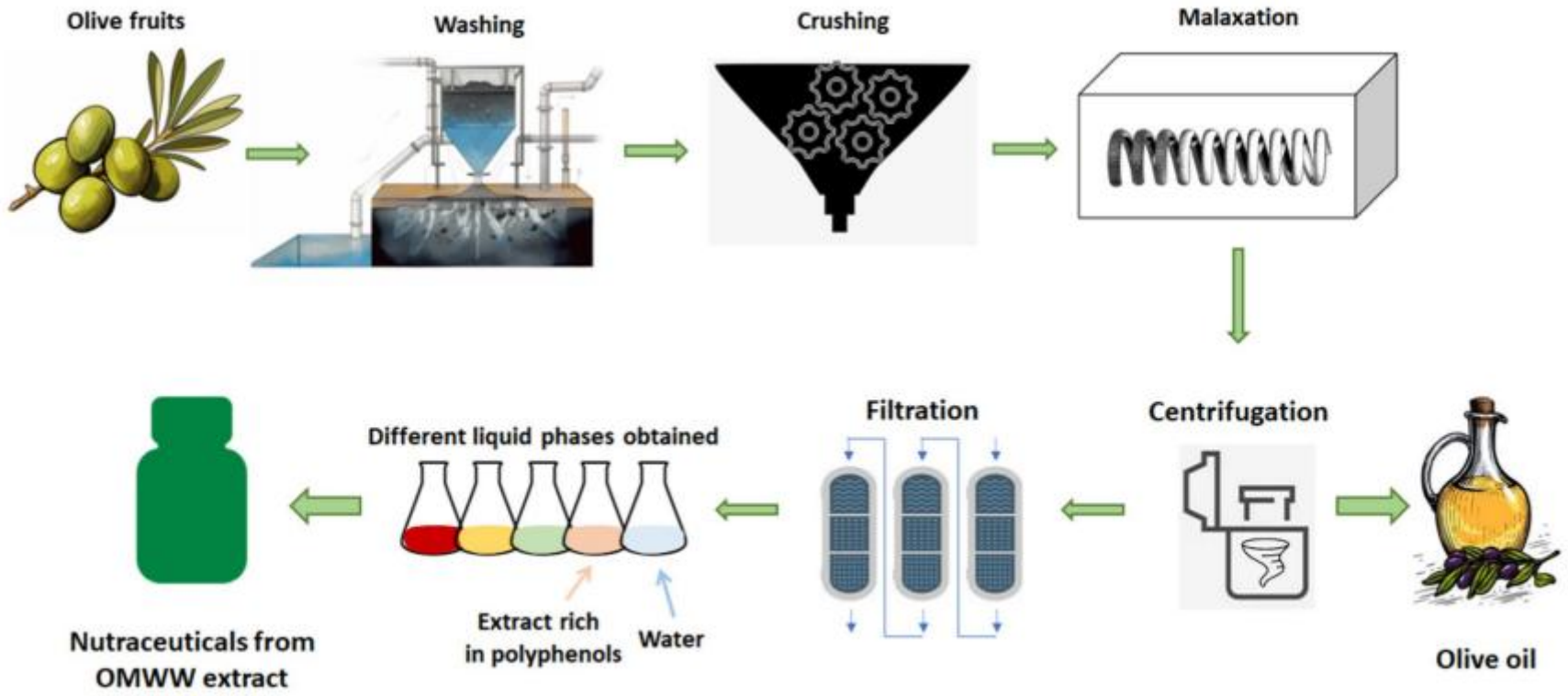

Figure 8. Extraction of active compounds from OMWW wastes of olive oil (from Albini *et al., Front. Nutr.* 2023, 10:1254947. doi: 10.3389/fnut.2023.1254947).

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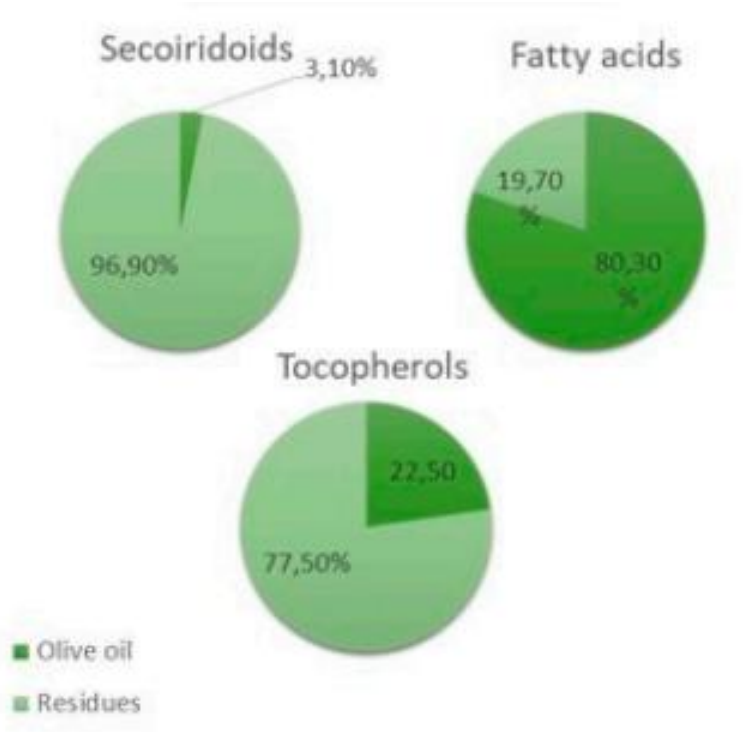
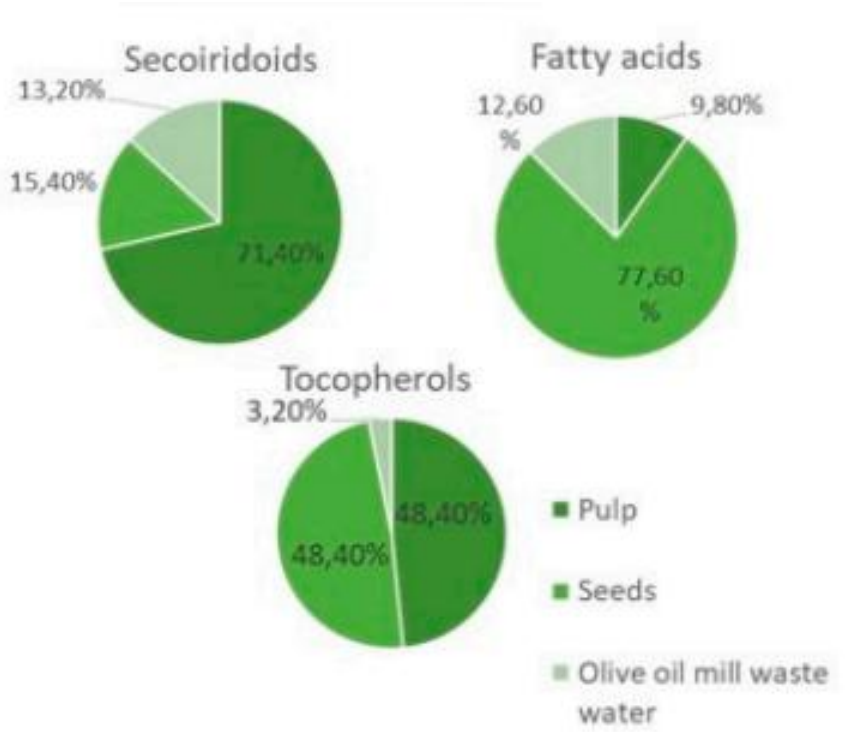
Example 1: By-products and wastes from Olives and Olive oil



Olive oil versus residues



Details within residues

- Antioxidant
- Anti-inflammatory
- Anti-diabetes
- Anti-hypertension
- Anticancer

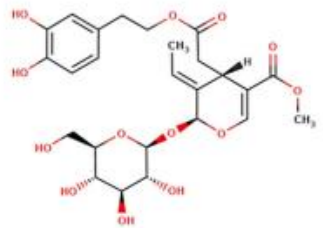
Figure 9. Distribution of compounds of interest between olive oil and residues (left image) and within residues part (right image) and their known biological activities (from Agaj *et al., Molecules,* 2022, 27, 8655. https://doi.org/10.3390/molecules27248655).

Example 1: By-products and wastes from Olives and Olive oil

Cells	OMWW extract		
	In vitro	*In vivo*	Combination with chemotherapy
Colon cancer	Suppression of proliferation, apoptosis, migration, invasion, adhesion, sprouting. Downregulation of VEGF and IL-8 (79). Negative regulation of NF-κB phosphorylation and TNF-α levels. Increase of PPARγ (80).	Slower growth of tumor mass (39).	Enhancement of the cisplatin and 5-FU drugs effect (39).
Lung cancer	Suppression of proliferation, induction of apoptosis, limitation of cell migration and invasion. Reduction in pro-angiogenic factors. Downregulation of CXCR4 and CXCL12 expressions (81).		
Prostate cancer	Reduction of cell viability, adhesion, migration, invasion, sprouting, and colonies formation (82).	Reduction of tumor size (39).	Enhancement of the cisplatin drug effect (39).
Breast cancer	Reduction of cell growth. Reduction size of breast cancer cell spheroids in combination with chemotherapy drugs (38).	Reduction of angiogenesis and enhancement of the T cell immune cell number (38).	Enhancement of the cisplatin, doxorubicin and 5-FU drugs effect (38).
Bladder cancer	Inhibition of growth and proliferation, both in chemo-sensitive and gemcitabine- and cisplatin-resistant tumour cells (83).		
Melanoma	Inhibition of A375 melanoma nodules growth in the melanoma skin model (33).		

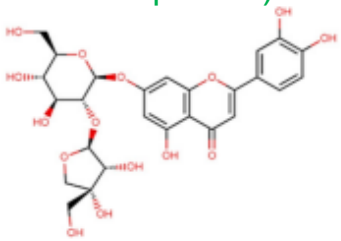
The table lists the OMWW extract's effect on several cancer cell types, both *in vivo* and *in vitro*, as well as in combination with currently available chemotherapeutic drugs.

Secoiridoids (phenolic compounds)



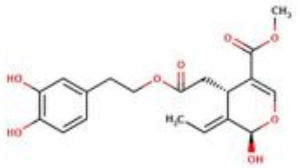
Oleuropein

$C_{25}H_{32}O_{13}$



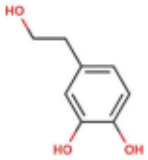
Luteolin 7-O-(2-apiosyl-glucoside)

$C_{26}H_{28}O_{15}$



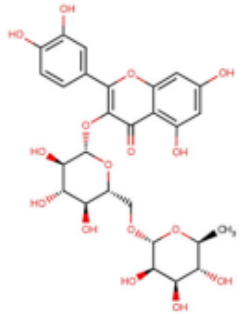
Oleuropein-aglycone

$C_{19}H_{22}O_8$



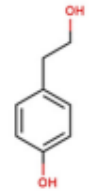
Hydroxytyrosol

$C_8H_{10}O_3$



Rutin (Quercetin 3-O-rutinoside)

$C_{27}H_{30}O_{16}$



Tyrosol

$C_8H_{10}O_2$

Figure 10. Anticancer effect of OMWW extracts demonstrated *In vitro* and *in vivo* and molecules potentially involved (from Albini *et al., Front. Nutr.* 2023, 10:1254947. doi: 10.3389/fnut.2023.1254947).

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Example 1: By-products and wastes from Olives and Olive oil

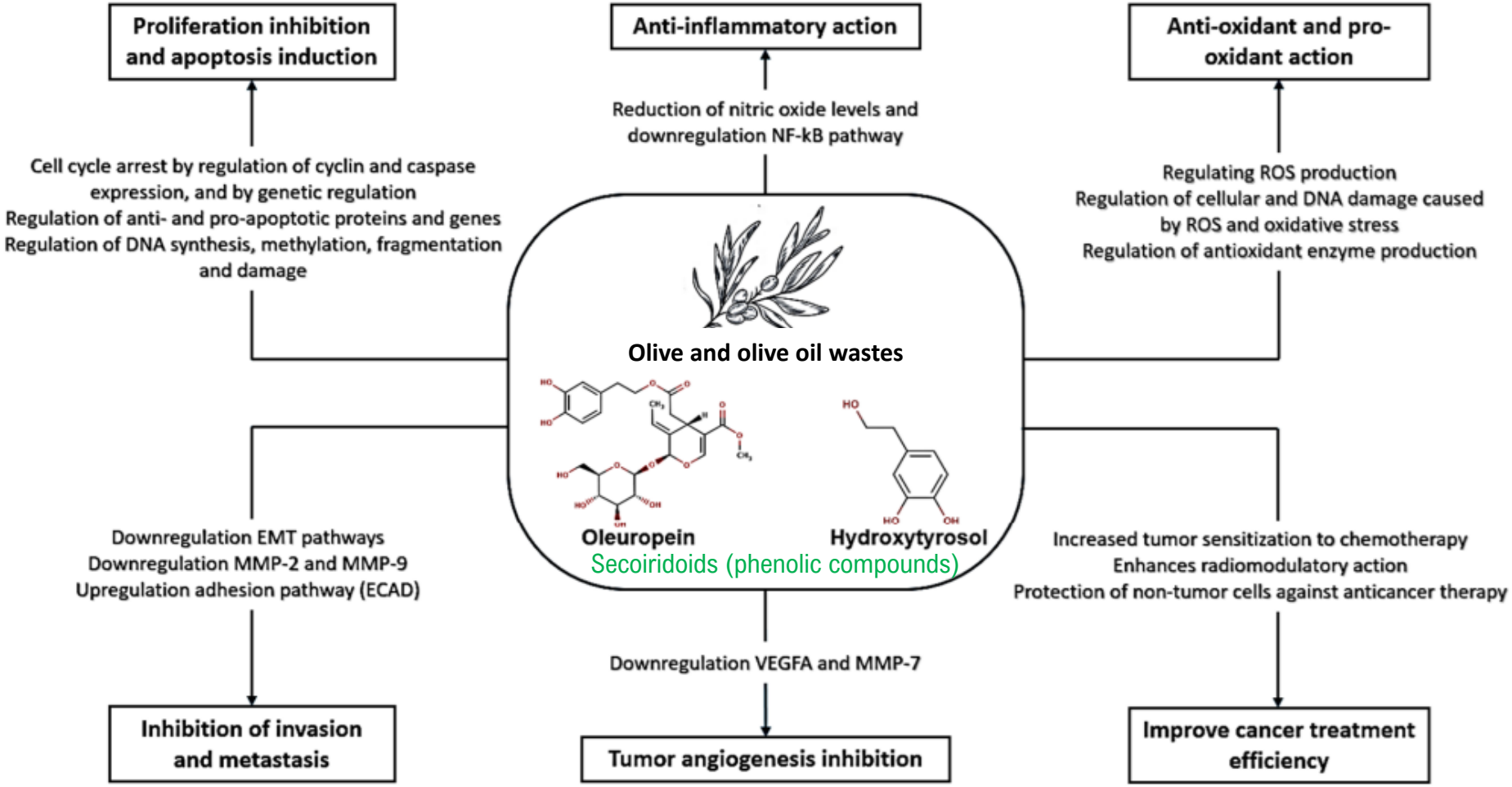

Figure 11. Compounds of interest extracted from olive and olive oil wastes (from Pessoa *et al., Molecules,* 2024, 29, 4249, https://doi.org/10.3390/molecules29174249).

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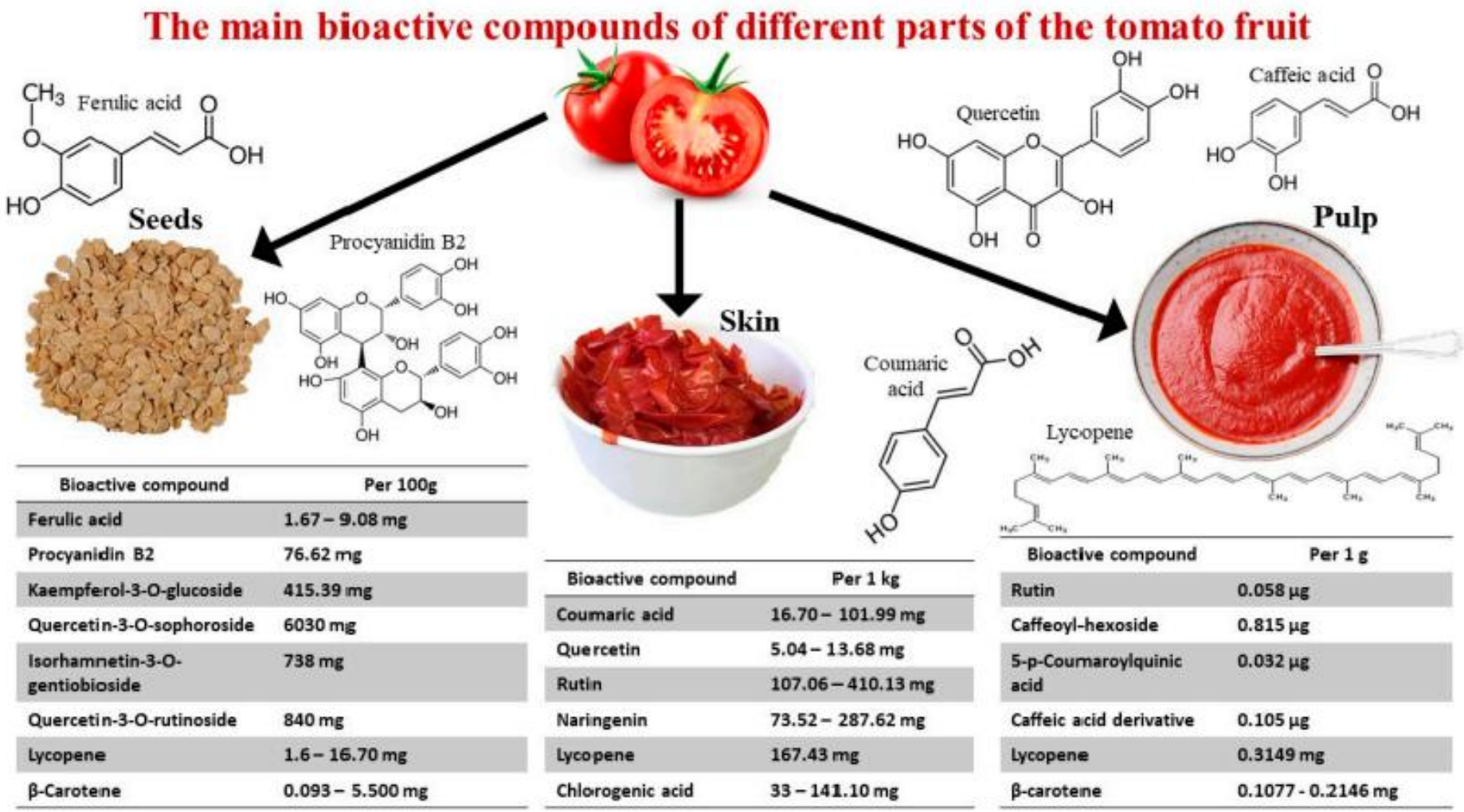
Example 2: By-products and wastes from Tomato



Bioactive compound	Per 100g
Ferulic acid	1.67 – 9.08 mg
Procyanidin B2	76.62 mg
Kaempferol-3-O-glucoside	415.39 mg
Quercetin-3-O-sophoroside	6030 mg
Isorhamnetin-3-O-gentiobioside	738 mg
Quercetin-3-O-rutinoside	840 mg
Lycopene	1.6 – 16.70 mg
β-Carotene	0.093 – 5.500 mg

Bioactive compound	Per 1 kg
Coumaric acid	16.70 – 101.99 mg
Quercetin	5.04 – 13.68 mg
Rutin	107.06 – 410.13 mg
Naringenin	73.52 – 287.62 mg
Lycopene	167.43 mg
Chlorogenic acid	33 – 141.10 mg

Bioactive compound	Per 1 g
Rutin	0.058 µg
Caffeoyl-hexoside	0.815 µg
5-p-Coumaroylquinic acid	0.032 µg
Caffeic acid derivative	0.105 µg
Lycopene	0.3149 mg
β-carotene	0.1077 - 0.2146 mg

Figure 12. Main bioactive compounds of different tomato fruit parts, namely, seeds, skin/peel and pulp (from Agaj *et al., Molecules,* 2022, 27, 8655. https://doi.org/10.3390/molecules27248655).

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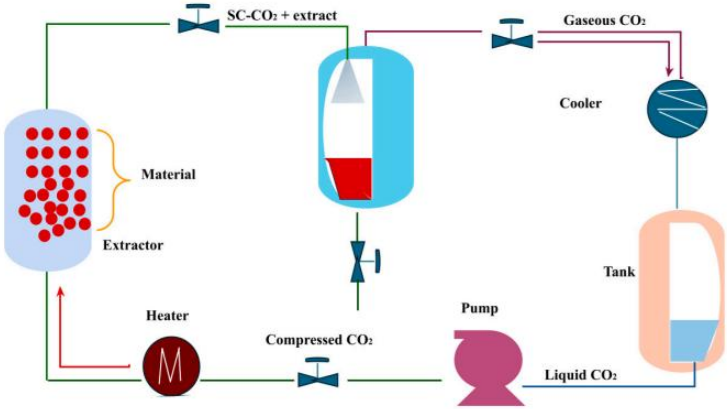
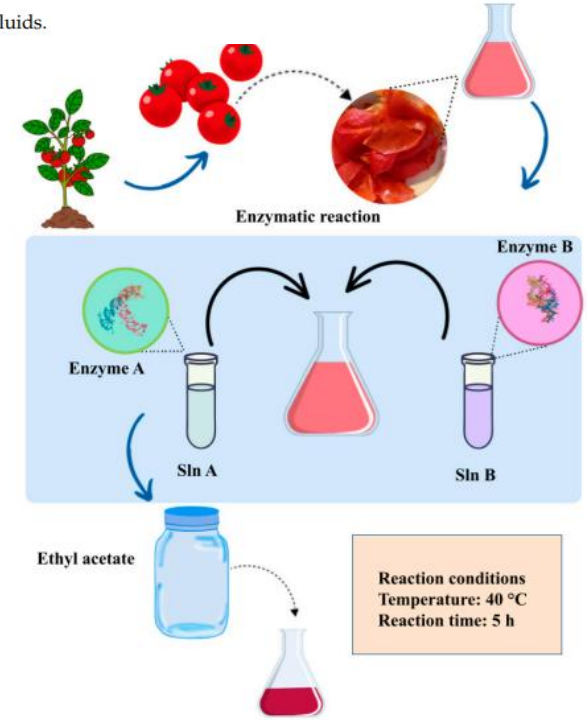
Example 2: By-products and wastes from Tomato

Technique	Principle of Operation	Operating Conditions	Lycopene Extraction	Environmental Considerations
Supercritical fluid extraction with CO_2 ($SC\text{-}CO_2$)	Employing carbon dioxide within supercritical extraction methods implements the supercritical fluid extraction (SFE) technique. This separation method utilizes a solvent fluid in a supercritical state to conduct the extraction process.	Pressure, temperature, CO_2 flow rate, and extraction time.	Lycopene extraction uses supercritical carbon dioxide ($SC\text{-}CO_2$) as a solvent. This process takes advantage of the supercritical properties of CO_2, acting as a highly efficient solvent to extract the lycopene-containing tomato oleoresin. $SC\text{-}CO_2$ penetrates the plant material during extraction and selectively dissolves the lycopene from the tomato matrix.	Employs environmentally friendly methods, eliminating the need for organic solvents and reducing storage, disposal, and environmental risks.
Enzyme-assisted extraction (EAE)	This method entails employing enzymes to enhance the effectiveness and specificity of extraction procedures. Through collaborative action with the enzymes inherent in the matrix, EAE enables a more effective breakdown of cellular structures, thereby aiding the liberation of the desired compounds.	Optimal enzyme conditions of temperature, pH, and dosage; optimal time-temperature conditions; plant material such as particle size, water content, chemical composition, and solvent-to-solid ratio.	Enzyme-assisted extraction is used to obtain lycopene. Enzymes such as cellulases, pectinases, and glucanases, individually or in combination, hydrolyze the bonds present in plant cell wall polysaccharides.	Mild conditions, extract quality, higher extraction yields, and higher quality.



Scheme of lycopene extraction by supercritical fluids.



Scheme of lycopene enzyme-assisted extraction.

Table 2. Main strategies to extract active compounds (here, lycopene as an example) from tomato wastes (from Bolaño *et al., Molecules,* 2024, 29, 3079. https://doi.org/10.3390/molecules29133079).

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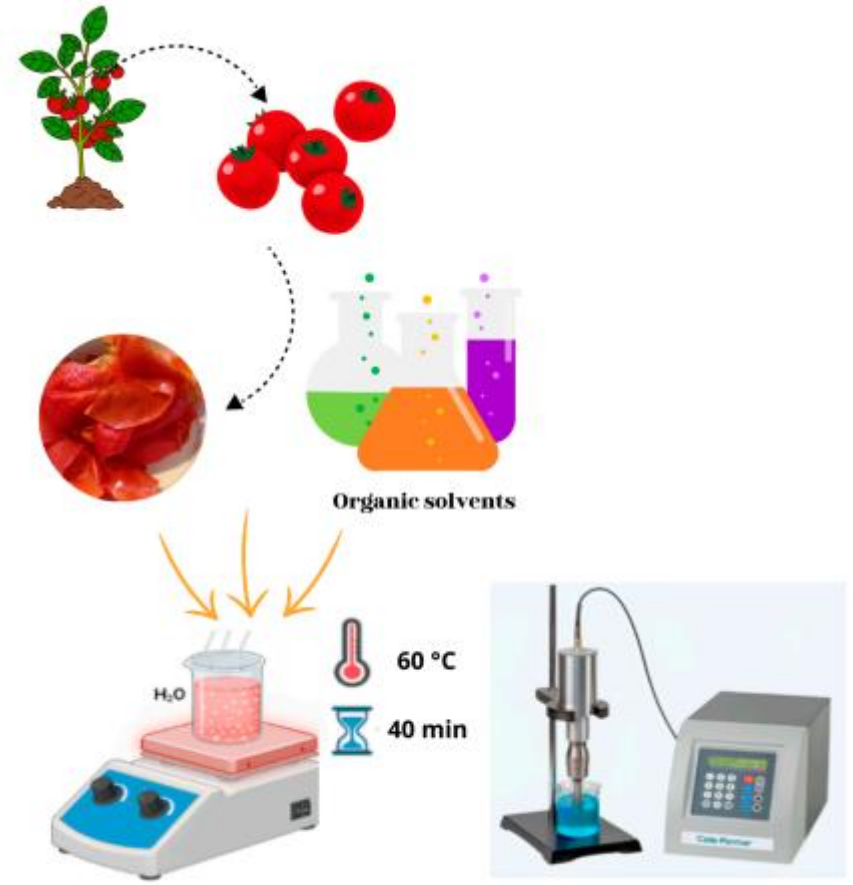
Example 2: By-products and wastes from Tomato

Technique	Principle of Operation	Operating Conditions	Lycopene Extraction	Environmental Considerations
Microwave-assisted extraction (MAE)	A technique in which microwave radiation is utilized to warm solvents in contact with a sample, facilitating the extraction of analytes from the sample matrix into the solvent.	Solid-to-solvent ratio, extraction time, and microwave power for extraction yield.	The application is the optimization of lycopene extraction from tomato peels using the microwave-assisted extraction (MAE) technique. The main objective is to improve the extraction efficiency of lycopene, a carotenoid present in tomato peel, which can be used as a natural colorant or bioactive ingredient.	MAE exploits a small number of solvents, so it is considered a "green" technique. Moreover, heating occurs selectively with much less energy loss in the environment.
Optimized mixed-polarity solvent mixtures	This method is frequently utilized in the food and pharmaceutical sectors due to its efficacy in extracting lipophilic compounds such as lycopene.	Extraction temperature, type of solvent used, stirring time, sample volume, and filtration method.	It is based on using homogeneous mixtures of solvents that exhibit two distinct properties: (a) high affinity for lycopene and (b) ability to swell the plant material and thus improve solvent penetration.	By optimizing solvent combinations, it is feasible to reduce the total amount required to perform an extraction or separation, reducing natural resource use and waste production.
Ultrasonic-assisted extraction	The ultrasound-assisted extraction (UAE) technique is based on acoustic cavitation, which occurs due to the propagation of mechanical waves generated by alternating high- and low-pressure cycles, known as compressions and rarefactions.	Properties of the solvent involved in extraction, such as viscosity and surface tension, alongside environmental factors like temperature and pressure.	Recent studies suggest that ultrasonic extraction enhances the extraction speed and boosts the yield of lycopene by approximately 10%.	Allow for the practical, cost-efficient, and eco-friendly extraction of bioactive components from plant sources. These technologies provide a sustainable and efficient means of producing top-quality plant-based products and offer a substantial competitive edge to businesses in the field.



Scheme of lycopene ultrasonic-assisted extraction.

Table 2. Main strategies to extract active compounds (here, lycopene as an example) from tomato wastes (from Bolaño *et al., Molecules,* 2024, 29, 3079. https://doi.org/10.3390/molecules29133079).

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Example 2: By-products and wastes from Tomato

Figure 13. Effect of tomato seed extract (TSE) on lipids. (a) TSE prevents the absorption of dietary fats, decreasing the plasma total cholesterol content and (B) TSE regulates the plasma fat content through LDLR (low-density lipoprotein receptors); it also reduces the plasma level of fats by enhancing the mitochondrial β-oxidation pathway (from Kumar *et al., Biomedicine & Pharmacotherapy,* 2021. https://doi.org/10.1016/j.biopha.2021.112018).

Example 2: By-products and wastes from Tomato

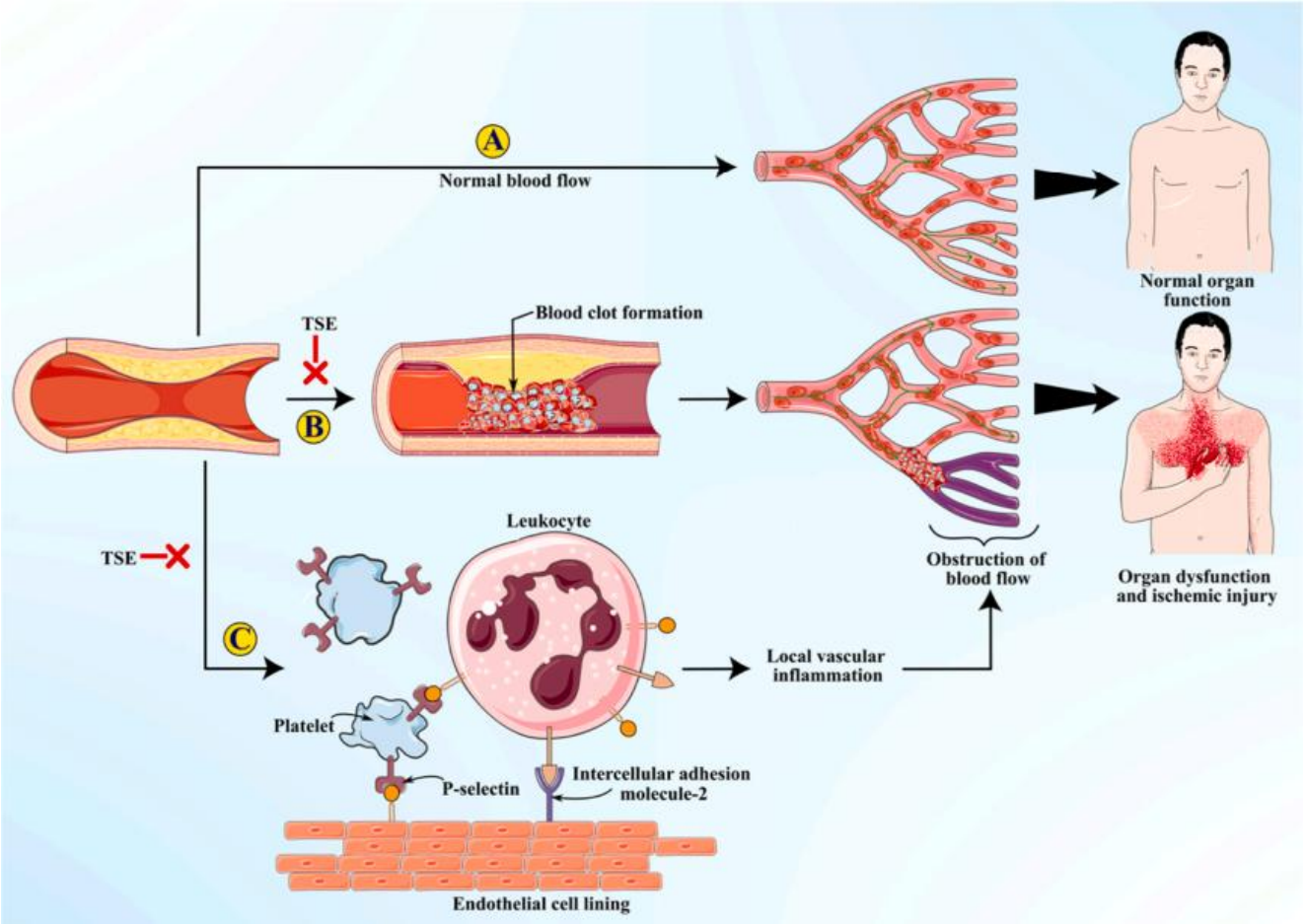

Figure 14. Anti-platelet activity/cardioprotective effects of tomato seed extract (TSE). (A) Normal blood flow in a healthy individual; (B) prevention of blood clot formation by TSE; (C) prevention of local vascular inflammation by TSE. Platelets adhere to the endothelial cell lining by P-selectins which, in turn, recruits leukocytes through intercellular adhesion molecule-2. This subsequently results in local vascular inflammation causing permanent or intermittent obstruction of blood flow, causing organ dysfunction and ischemic injury (from Kumar *et al., Biomedicine & Pharmacotherapy,* 2021. https://doi.org/10.1016/j.biopha.2021.112018).

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Example 2: By-products and wastes from Tomato

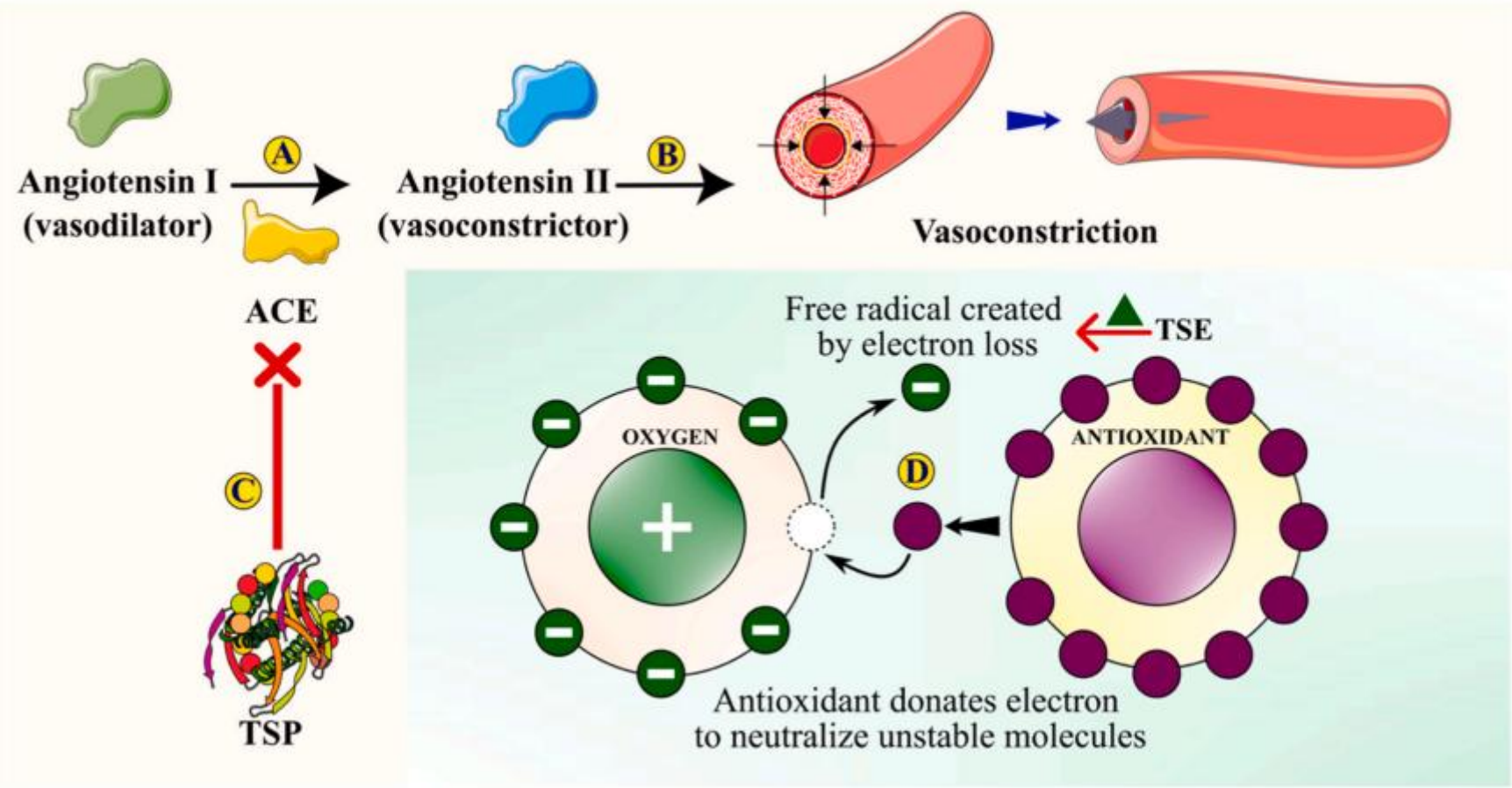

Figure 15. Control of hypertension through the renin-angiotensin system and its regulation through TSE. (A) Angiotensin-1 converting enzyme (ACE) mediates the conversion of angiotensin-1 (vasodilator) to angiotensin-2 (vasoconstrictor); (B) vasoconstriction of blood vessels through angiotensin-2 (vasoconstrictor); (C) blockage of ACE activity by TSP (tomato seed protein) for controlling blood pressure; (D) radical scavenging and antioxidant activity of TSE (from Kumar *et al., Biomedicine & Pharmacotherapy,* 2021. https://doi.org/10.1016/j.biopha.2021.112018).

Example 2: By-products and wastes from Tomato

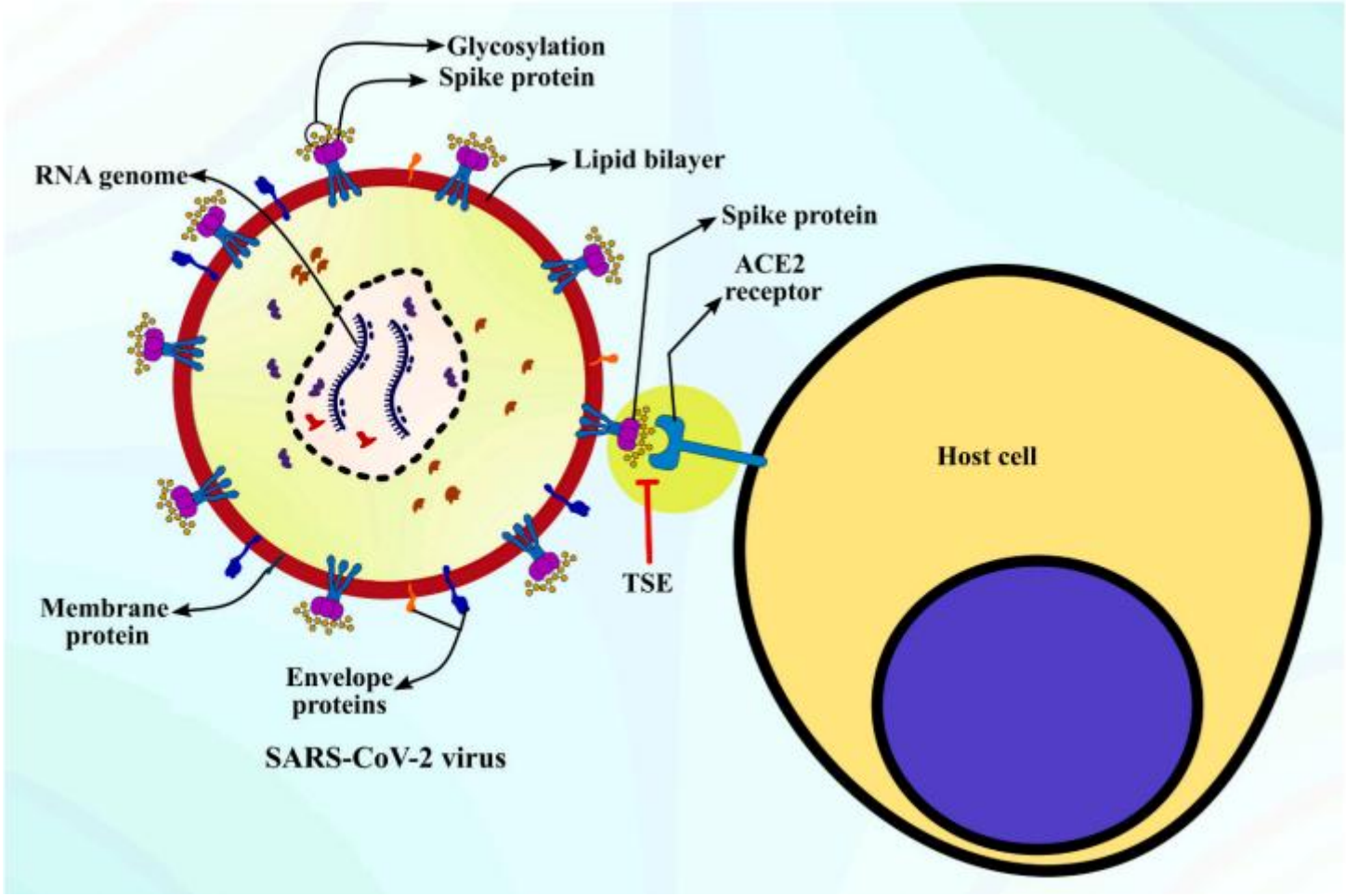

Figure 16. Inhibition of interaction between spike glycoproteins (S-protein) and host cell surface receptors angiotensin converting enzyme 2 (ACE-2) by tomato seed extract (TSE) (from Kumar *et al., Biomedicine & Pharmacotherapy,* 2021. https://doi.org/10.1016/j.biopha.2021.112018).

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Example 2: By-products and wastes from Tomato

Type of Cancer	Function of Lycopene	Administration	Studies
Prostate cancer	Lycopene inhibits DNA synthesis, which could significantly decrease the proliferation and growth of cancer cells in primary epithelial prostate cancer.	Lycopene could be used as a therapeutic adjunct in patients with prostate cancer to improve apoptosis and prevent the progression of cancer cells.	Lycopene has demonstrated efficacy in treating locally advanced prostate cancer, reducing mortality in high-risk men, and slowing the progression of the disease.
Breast cancer	Lycopene decreased cell growth, induced cell cycle arrest, and caused changes in mitochondrial membranes and DNA fragmentation. It showed no hemolytic activity and had low toxicity against peritoneal macrophages.	Supplementation with lycopene complexes and other antioxidants reduces skin toxicity during radical radiation therapy.	In an animal model, lycopene supplementation and other antioxidants demonstrated the potential to reduce skin toxicity during radical radiotherapy treatment for breast cancer.
Lung cancer	Inhibits induced pulmonary toxicity by preventing inflammation and macrophage infiltration.	Adjuvant therapy.	Lycopene has been studied in laboratory and animal models of lung cancer cells. It shows cell growth-inhibiting properties and promotes apoptosis.
Ovarian cancer	The consumption of lycopene through diet has been associated with a lower risk of ovarian cancer, indicating its potential as a preventive agent against ovarian carcinogenesis.	Lycopene, administered orally as a preventive measure, significantly reduced intraperitoneal metastatic burden and, when given as a treatment, significantly reduced the tumor burden of ovarian cancer.	Lycopene intake has decreased the occurrence and size of ovarian tumors in laying hens. This effect is attributed to its antioxidant and anti-inflammatory properties, which regulate signaling pathways in ovarian cells.
Stomach cancer	Treatment with lycopene suppresses the proliferation of gastric cancer cells by inducing cell cycle arrest in the G0–G1 phase. Moreover, lycopene prevents the upregulation of p53 expression in gastric mucosa exposed to cigarette smoke.	The administration of lycopene at doses of 50, 100, or 150 mg/kg of body weight led to an anticipated increase in antioxidant enzymes (SOD, CAT, GSH-Px). It also increased cytokine levels (IL-2, IL-4, IL-10, TNF-α) and antibodies (IgG, IgA, IgM).	Lycopene intake protects against stomach cancer, regardless of *Helicobacter pylori*. Its beneficial effect in animal models of gastric and esophageal cancer lies in modulating the proliferation and apoptosis of tumor cells induced by carcinogens.

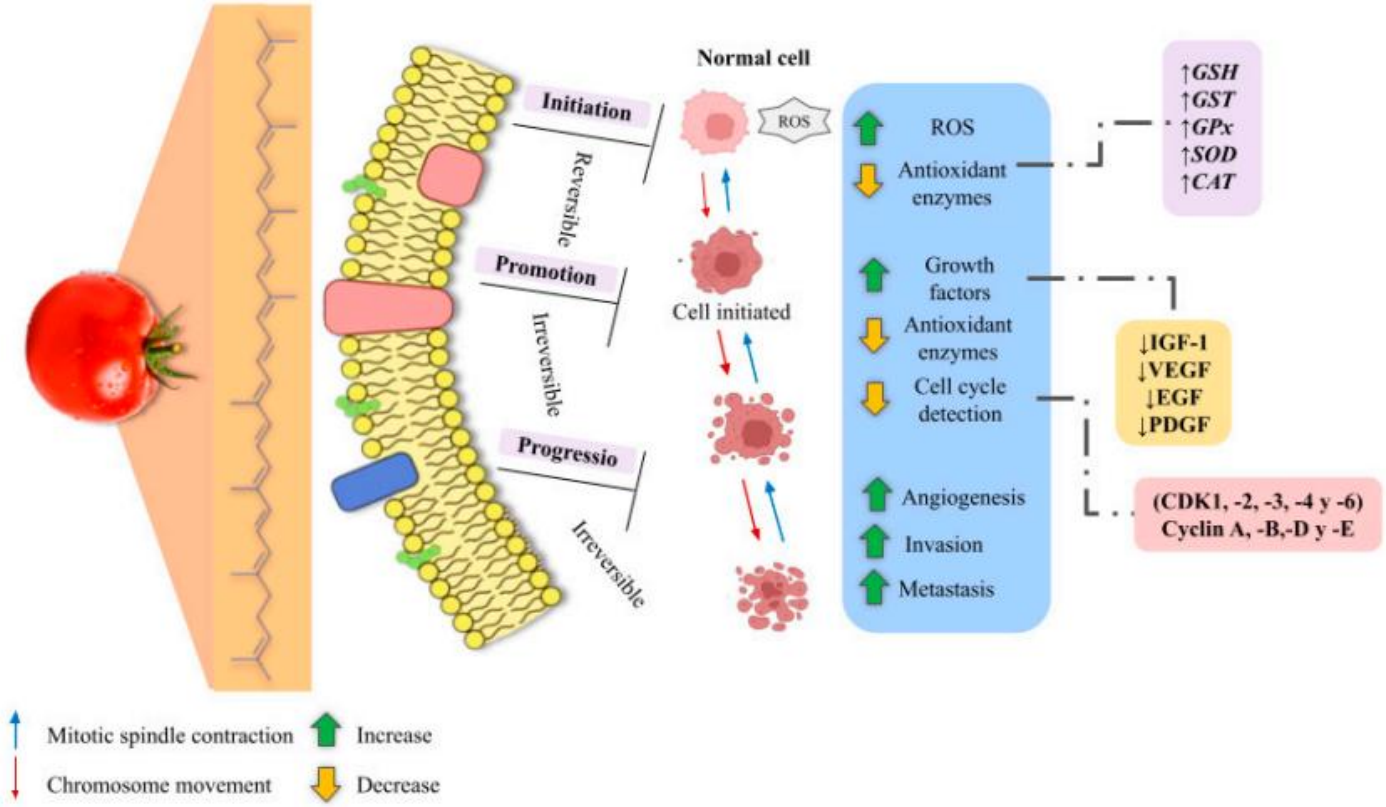

Figure 17. Anticancer effects of lycopene (carotenoid) and mechanisms involved (from Bolaño *et al.*, *Molecules*, 2024, 29, 3079. https://doi.org/10.3390/molecules29133079)

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Example 2: By-products and wastes from Tomato

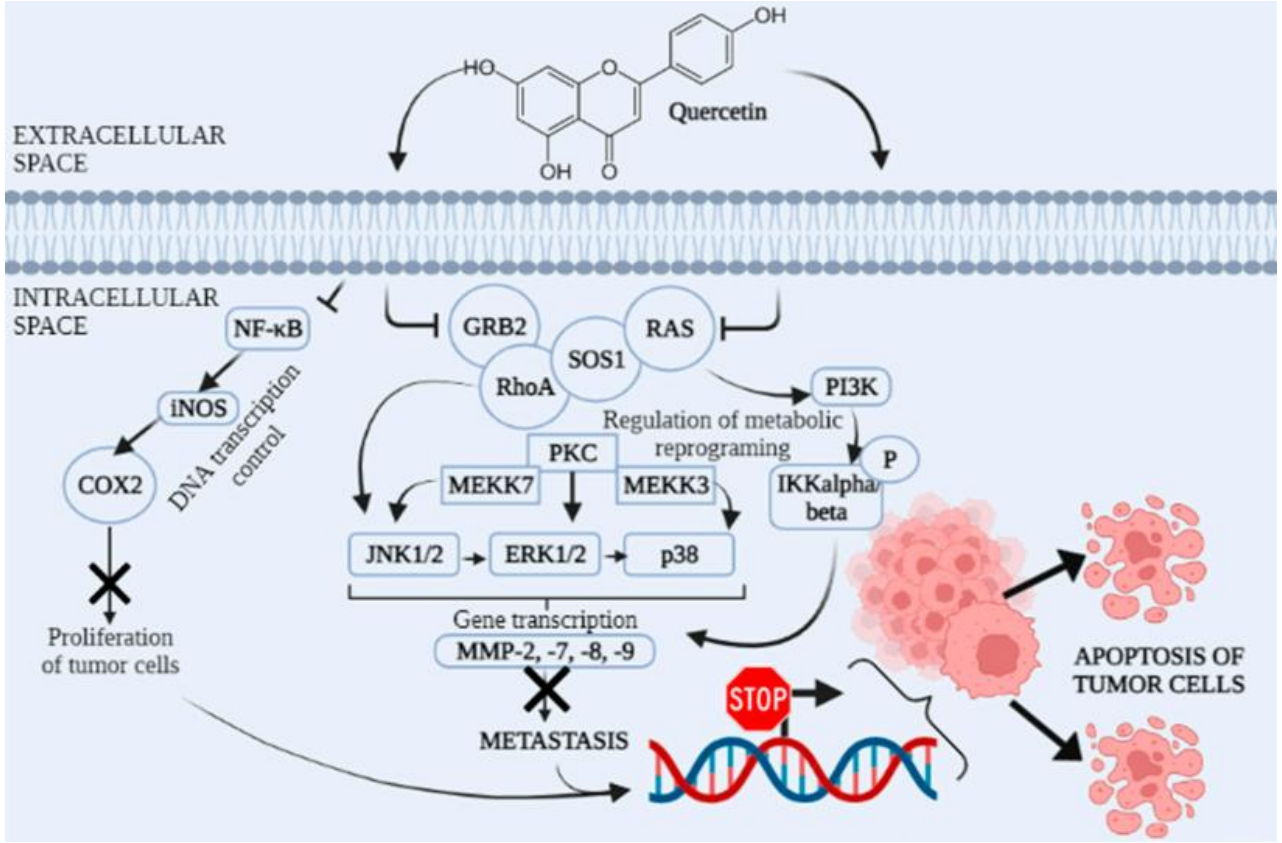

Figure 18. Quercetin anti-inflammatory and antitumor mechanisms of action. Quercetin inhibits NF-κB (Nuclear factor kappa-lightchain-enhancer of activated B cells), iNOS (Inducible nitric oxide synthase) and COX2 (Cyclooxygenase 2). It results in blockade of proliferation of inflammation and cell division. Moreover, quercetin inhibits interaction of GRB (Growth factor receptor-bound protein), RhoA (Ras homolog family member A), SOS1 (Son of Sevenless 1) and RAS (Rat sarcoma virus), which prevents further metabolic reprograming. That includes inhibition of other metabolic molecules; PKC (Protein kinase C), MEKK-3, -7 (Mitogen-activated protein/ERK kinase -3, -7), JNK1/2 (c-Jun N-Terminal Protein Kinase 1/2), ERK1/2 (Extracellular signal-regulated kinase 1/2), p38 (Mitogen-activated protein kinase), PI3K (Phosphoinositide 3-kinase), IKKalpha/beta (Inhibitor of nuclear factor kappa-B kinase subunit beta). It also inhibits MMP-2, -7, -8, and -9 (Matrix metalloproteinases) involved in metastasis. Finally, quercetin induces tumour cell apoptosis (from Agaj *et al., Molecules,* 2022, 27, 8655. https://doi.org/10.3390/molecules27248655).

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Example 3: By-products and wastes from Tuna

- **Unsaturated fatty acids** (PUFA, EPA, DHA) (anti-diabetes, anti-inflammatory, anti-hypertension, cosmetic)
- **Gelatin and Collagen** (antioxidant, cosmetic)
- **Polysaccharides** (antioxidant, anti-microbial, anti-viral, anti-hypertension, anticancer, cosmetic)
- **Bioactive peptides** (antioxidant, antimicrobial, anticancer, and others)
- **Minerals** (calcium, magnesium, iron, phosphorus)

Figure 19. Fishes and Seafood production in 2016 (from Mutalipassi *et al., Foods,* 2021, 10, 1495. https://doi.org/10.3390/foods10071495).

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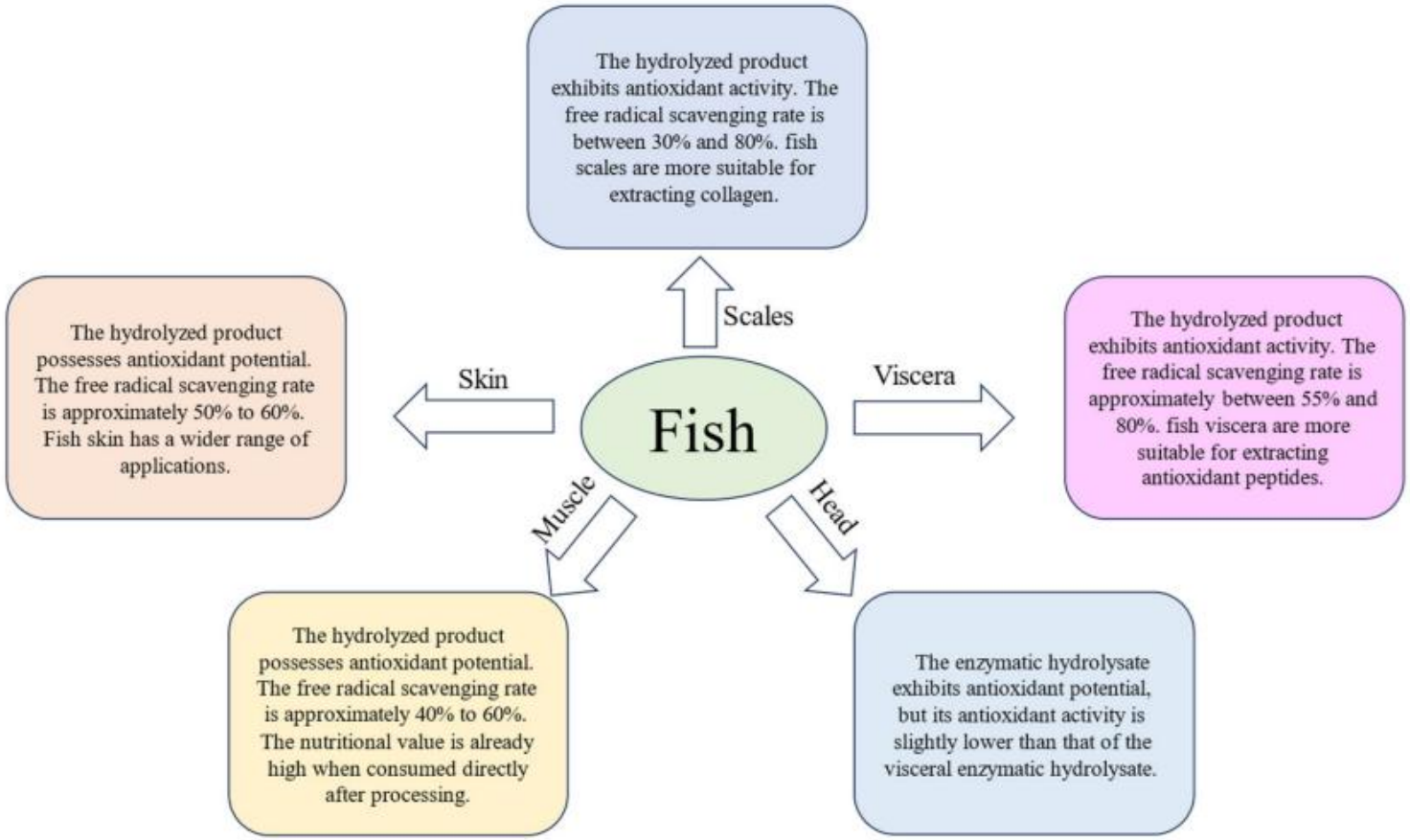
Example 3: By-products and wastes from Tuna

Bioactive compounds can be extracted from all parts of the fishes



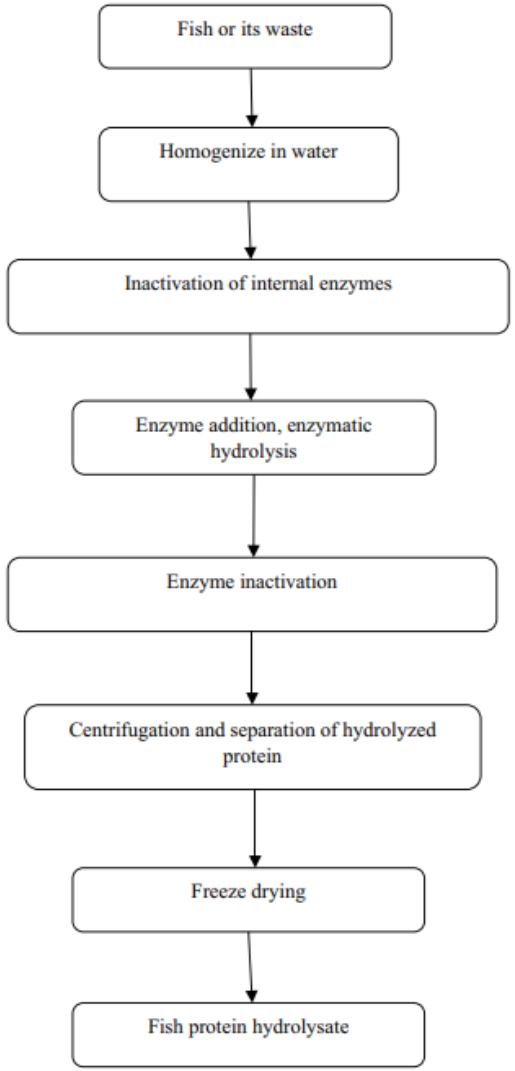


Figure 20. Extraction of antioxidant peptides from fish parts (from Liu *et al., Metabolites,* 2024, 14, 561. https://doi.org/10.3390/metabo14100561).

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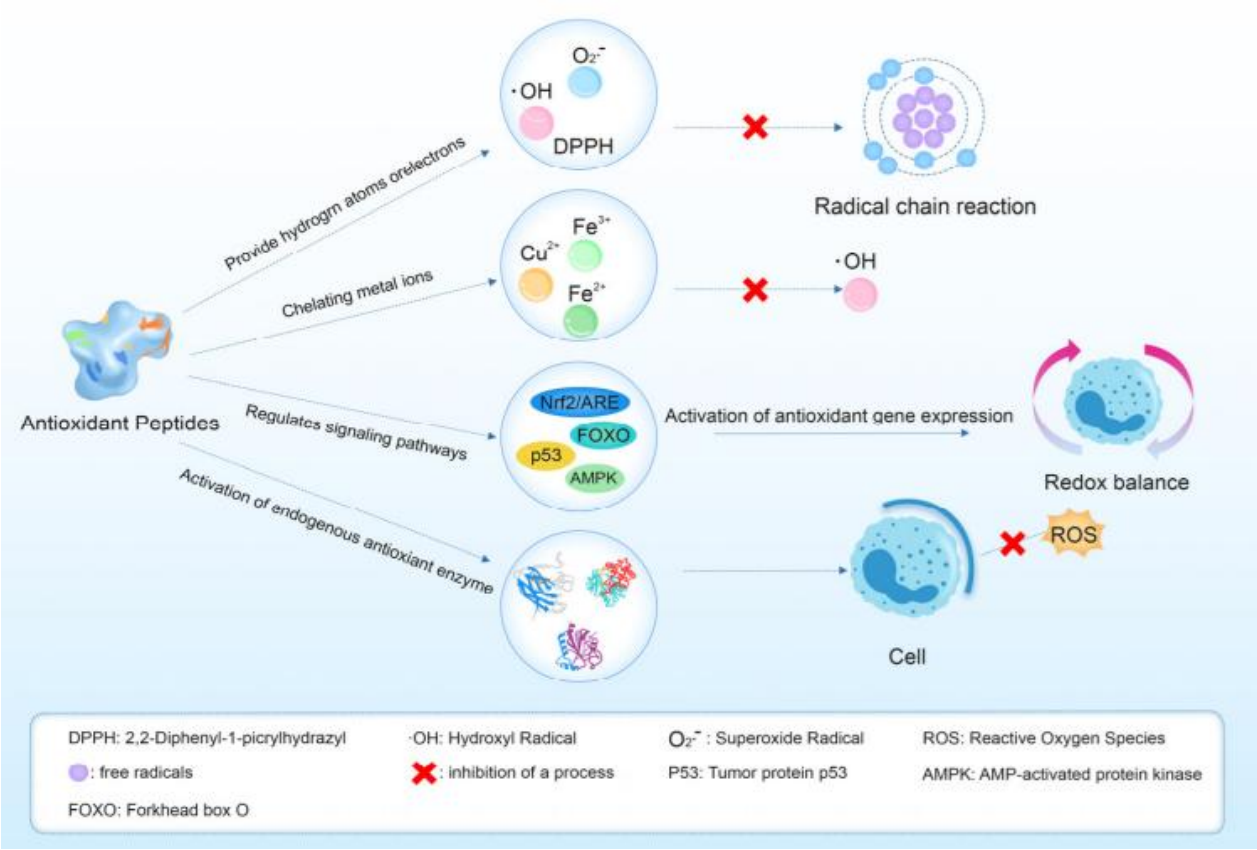
Example 3: By-products and wastes from Tuna



Source	Extraction Site	Active Substance Name	Mechanism of Action
Bigeye tuna	Skin and bones	TSCP, TBCP	Inhibition of signaling pathways
Yellowfin tuna	Skin	PH, PWG, EL, AH, IR, HL	Inhibition of MPO activity
Yellowfin tuna	Trimmings	ACGSDGK	Inhibition of MPO activity
Skipjack Tuna	Bones	GADIVA, GAEGFIF	Scavenging free radicals
Skipjack Tuna	Dark muscle	YENGGG, EGYPWN, YIVYPG, WGDAGGGYY	Scavenging free radicals
Bigeye tuna	Dark muscle	APTDM	Scavenging free radicals
Skipjack Tuna	Skin	STG-AH	Scavenging free radicals
Skipjack Tuna	Roes	AEM, QDHK, YEA, AEHNH, YVM	Scavenging free radicals

Figure 21. Tuna wastes and by-products as a source of antioxidant peptides (from Cheng *et al., Mar. Drugs,* 2025, 23, 293. https://doi.org/ 10.3390/md23070293).

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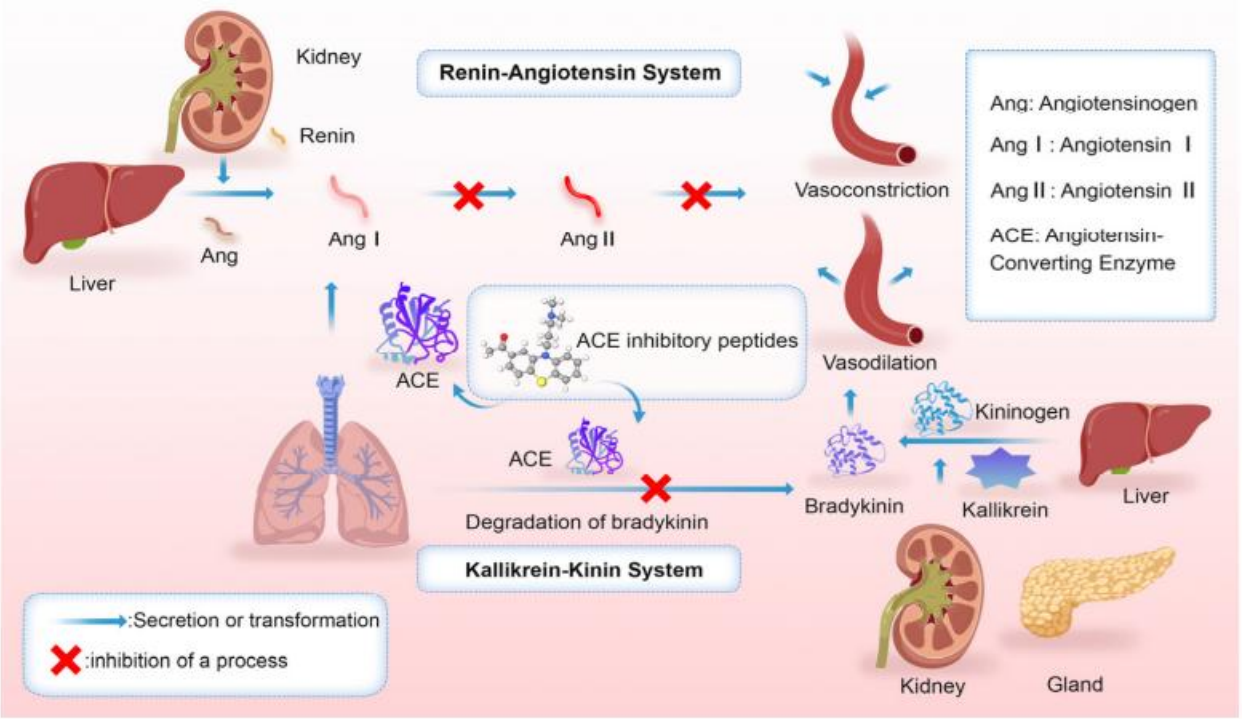
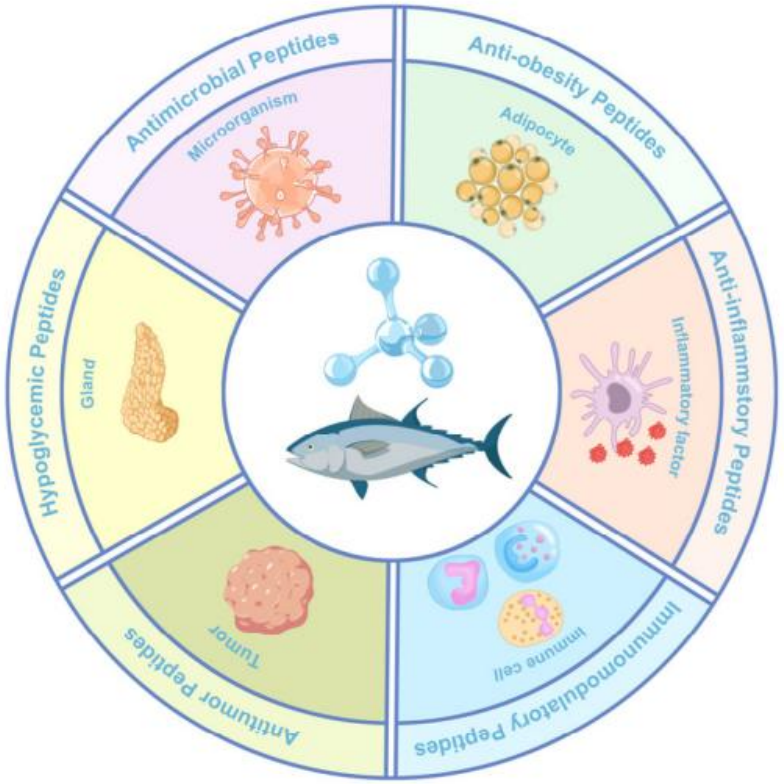
Example 3: By-products and wastes from Tuna



Source	Extraction Site	Active Substance Name	IC50
Atlantic tuna	Muscle	LTGCP, YPKP	64.3 μM, 139.6 μM
Skipjack Tuna	Roes	MLVFAV	3.07 μM
Skipjack Tuna	Dark muscle	FPPDVA	87.11 ± 1.02 μM
Bigeye tuna	Dark muscle	WPEAAELMMEVDP	21.6 μM
Skipjack Tuna	Dark muscle	MWN, MEKS, MKKS, LPRS	0.328 ± 0.035, 0.527 ± 0.030, 0.269 ± 0.006, 0.495 ± 0.024 mg/mL
skipjack tuna	Milts	ICY, LSFR, IYSP	0.48, 0.59, 0.76 mg/mL
Skipjack Tuna	Muscle	SP, VDRYF	0.06 ± 0.01, 0.28 ± 0.03 mg/mL

Figure 22. Tuna wastes and by-products as a source of antihypertension peptides (from Cheng *et al., Mar. Drugs,* 2025, 23, 293. https://doi.org/10.3390/md23070293).

Example 3: By-products and wastes from Tuna



Source	Extraction Site	Active Substance Name	Activity
Yellowfin tuna	Dark muscles	KPLSeCPK	α-glucosidase inhibition
Skipjack tuna	Flesh of fish	FQLSAER, GEVDDSIQE, YEAFVK, KSIDDVEE	Umami peptide
Bluefin tuna	Skin	GPSGGGYDV	DPP-IV inhibitory peptide
Bluefin tuna	Skeletal myosin	LADW, MEIDD, VAEQE, EEAEGT	Umami peptide
Yellowfin tuna	Trimmings	HIAEEADRK AEQAESDKK	Immunomodulatory peptide
Skipjack tuna	Muscles	ACECD	XODI peptide
Skipjack tuna	Skin	SJGAP	Antimicrobial peptide
Bluefin tuna	Skeletal myosin	EEAGGATAAQIEM	Antiviral peptide
Yellowfin tuna	Pancreas	LLDF	Ache inhibitory peptide
Skipjack tuna	Dark muscles	APP, PPP, DPLL, EAVP, EAIP	DPP-IV inhibitory peptide

Figure 23. Other bioactive peptides found in Tuna wastes and by-products (from Cheng *et al., Mar. Drugs,* 2025, 23, 293. https://doi.org/ 10.3390/md23070293).

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Example 3: By-products and wastes from Pomegranate

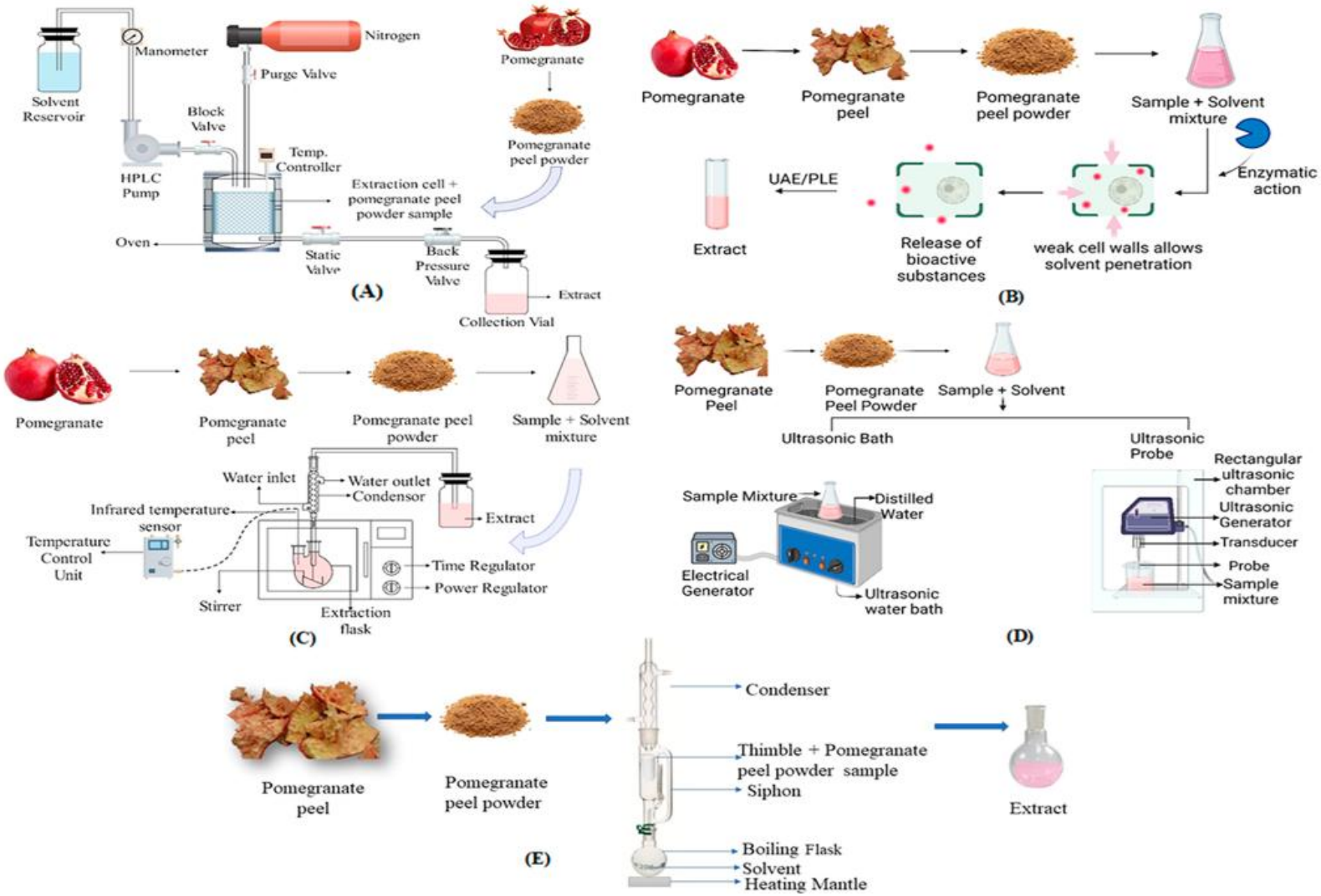

Figure 24. Methods of extraction from Pomegranate peel: (A) Pressurized Liquid Extraction (PLE), (B) Enzyme-Assisted Extraction (EAE), (C) Microwave-Assisted Extraction (MAE), (D) Ultrasound-Assisted Extraction (UAE), and (E) Soxhlet extraction(from Singh *et al., ACS Omega,* 2023, 8, 35452−35469, DOI: 10.1021/acsomega.3c02586).

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Example 3: By-products and wastes from Pomegranate

Table 1. Proximate Composition and Vitamin and Mineral Content of Pomegranate Peel Powder[7–13]

Parameter	Value
Proximate Composition (g/100 g)	
Moisture	8.43–13.80
Protein	3.24–3.46
Fat	0.55–3.36
Crude fiber	17.43–35.19
Ash	3.35–6.07
Carbohydrates	59.52–61.34
Vitamins (mg/100 g)	
Vitamin A	0.16–0.18
Vitamin E	3.99–4.13
Vitamin C	12.90–13.26
Vitamin B1	0.12–0.14
Vitamin B2	0.07–0.09
Minerals (mg/100 g)	
Calcium	338.50–342.00
Potassium	146.40–164.30
Sodium	64.63–68.00
Phosphorus	117.90–120.00
Iron	5.93–10.25

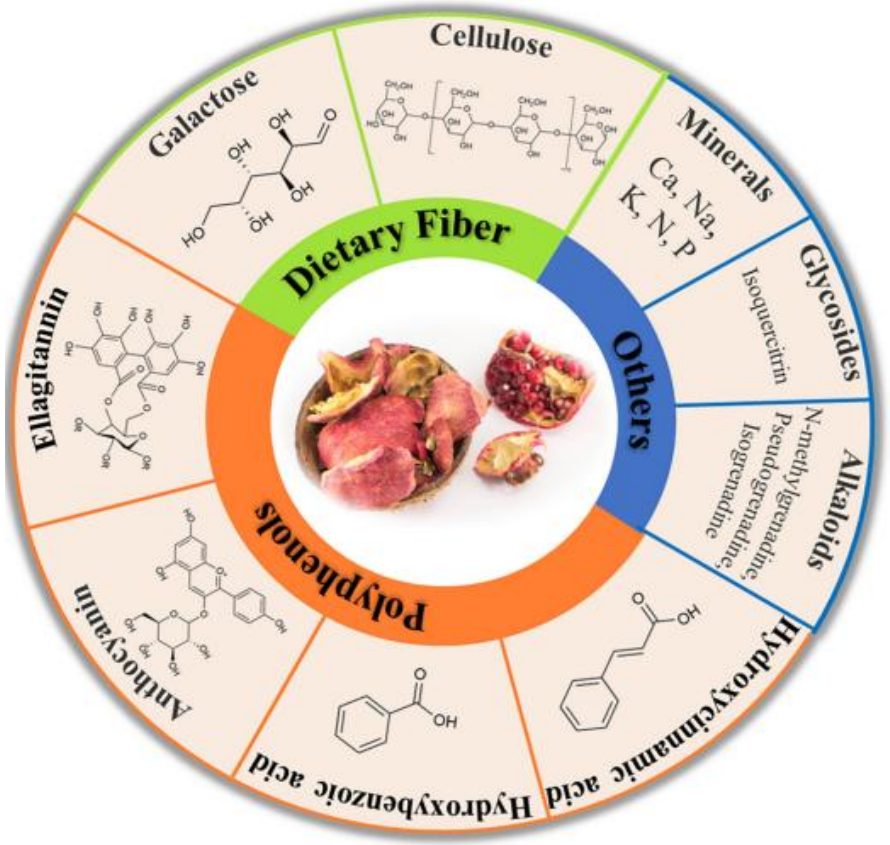

Table 2. Quantitative Analysis of Phytochemicals Present in Pomegranate Peel[8,12,19–21]

Compound[a]	Conc (mg/100 g)
Total phenolic content (GAE)	4892.00–6138.20
Total flavonoid content (QE)	529.50–862.50
Ellagic acid	44.19–52.03
Catechin	850.00–892.00
Gallic acid	125.80–128.10
p-Coumaric acid	14.00–17.64
Quercetin	5
Ferulic	5.00–6.11

[a]GAE, gallic acid equivalent; QE, quercetin equivalent.

Figure 25. Valuable molecules found in Pomegranate peel (from Mo *et al., Front. Nutr.* 2022, 9:887113. doi: 10.3389/fnut.2022.887113 and Singh *et al., ACS Omega,* 2023, 8, 35452−35469, DOI: 10.1021/acsomega.3c02586).

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Example 3: By-products and wastes from Pomegranate

Pharmacological activity	Plant part	Model (cell/animal/humans)	Dosage/conc	Effects
Cardio-protective	Pomegranate extract capsule	Human intervention study (*in vivo*)	Walnuts (30 g/day) Pomegranate extract capsule (450 mg/day) Mixed nuts (30 g/day)	Urolithin metabotype A showed positive correlation with ApoA-I. Urolithin metabotype A phenotype protects against CVDs compared to urolithin metabotype phenotype B.
	Hydroethanolic PPE extract	Apoe$^{-/-}$ mice (*in vivo*)	200 mg/kg	Improved metabolic profile (decreased total cholesterol, triglycerides, plasma insulin, blood glucose levels, improved glucose tolerance). Reduction of proinflammatory cytokines and plaque necrosis.
	Pomegranate peel polyphenols	Human hepatic L-02 cells (*in vitro*)	10, 20, and 40 μg/mL (pomegranate peel polyphenols, punicalagin, pomegranate ellagic acid)	Decreased total cholesterol and increased total bile acid content. Up-regulation of PPARγ, ABCA1, and CYP7A1 mRNA expression.
	PPE	Wistar albino rats (*in vivo*)	50 or 100 mg/kg body weight (PPE), 1 mg/kg body weight (ellagic acid), and 7 mg/kg body weight (punicalagin)	Reduced TC, TAG, LDL cholesterol, VLDL cholesterol, atherogenic index of plasma, atherogenic coefficient. Improved activity of GR, SOD, CAT, and GSH. Elevated serum PON1 activity.
Anticancer	Pomegranate peel polyphenols	Human hepatoma cells HepG2 (*in vitro*)	50 and 100 μM (punicalagin and ellagic acid)	Reduced the HepG2 cells survival rate. Punicalagin and ellagic acid arrested the cells in the S phase and G0/G1 phase of the cell cycle resulting in apoptosis. Increased caspase 3/9 activity and apoptosis related genes.
	PPE	MCF-7 and MDA-MB-231 cells (*in vitro*)	Punicalagin concentration (0, 12.5, 25, 50, 100 μM)	Punicalagin (>50 μM) inhibited viability, migration, and invasion of MDA-MB-231 and MCF-7 cells. A substantial decrease in the expression of GOLPH3, MMP-9, MMP2, and N-cadherin and an increase in the expression of E-cadherin were observed.
	PPE	DU145, PC3, TRAMP-C1 cell lines (*in vitro*)	0, 12.5, 25, 50, 100, and 200 μg/mL	PPE suppressed growth on prostate cancer cells, increased expression of pro-apoptotic Bax, and decreased expression of antiapoptotic Bcl2. Up-regulation of MMP2/9 expression and mitochondrial mediated apoptosis in TRAMP-C1.
	PPE	BCPAP and TPC-1 cell lines (*in vitro*)	0, 12.5, 25, 50, 100, 200 μg/mL	PPE considerably reduced proliferation in cell lines, thus exhibiting cytotoxic and cytostatic activity. Concentration-dependent apoptosis was induced in cancer cell lines. PPE reduced the mitochondrial membrane potential, thereby inducing apoptosis.
	PPE	Female BALB/c nude mice (*in vivo*)	125 mg/kg and 62.5 mg/kg body weight	Tumor growth was inhibited by preventing metastasis, promoting apoptosis, and reducing the proliferation of cells.
Antimicrobial	Pomegranate peel polyphenols	*Ralstonia solanacearum* model strain GMI1000 (*in vitro*)	0, 5, 10, and 15 μg/mL	Growth curve was steady in treated cultures. Cell wall and cell membrane were detached. Bacterial motility was reduced. Attachment of punicalagin with functional domains of PhcA resulted in disarranged network eventually leading to bacterial damage.
	PPE	Wistar rats (*in vivo*)	125, 250, and 500 mg/kg/d BW	Decreased the growth of *Candida albicans*. Compared to nystatin, pomegranate peel exhibited 100% efficacy at all doses. Preserved the natural structure of epithelium, muscular core, and lamina propria in tongue.
	PPE	Swiss albino mice (*in vivo*)	100 μL (300 mg/kg)	ELISA revealed a gradual reduction in *Giardia* antigen in the feces of mice treated with PPE. A decrease in the cyst formation with a simultaneous increase in cure rate was observed in the experimental group.
Wound healing	Pomegranate pele extract	Rats (*in vivo*)	5 g PPE/100 g gel	Increase in collagen content, hydroxyproline levels, wound contraction, expression of EGF, VEGF, and TGF-β1, epithelialization, and granulation was observed in the treatment group.
Anti-inflammatory	Ethanolic PPE	Swiss Webster mice (*in vivo*)	240 and 480 mg/kg/d (Doses-1 and Doses-2, respectively)	Reduction in COX-2 and iNOS expression via inhibition of the NF-κB pathway was reported.
	Pomegranate peel polyphenols	RAW264.7 macrophage (*in vitro*)	1, 10, 100 μg/mL (pomegranate peel polyphenols) 1, 10, 50 μM (punicalagin and ellagic acid)	Test polyphenols down-regulated LPS induced NO and PGE2 generation. Decreased pro-inflammatory cytokines and inhibited MAPKs pathway.

Table 3. Valuable molecules found in Pomegranate peel and their biological activities (from Singh *et al., ACS Omega,* 2023, 8, 35452−35469, DOI: 10.1021/acsomega.3c02586).

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Example 3: By-products and wastes from Pomegranate

Unpublished personal data obtained in collaboration with Prof Akram Hijazi and his students (Mohamad Ataya, *Houssein Bazzi,* Marwa Fouani) (from Lebanese University, Lebanon).

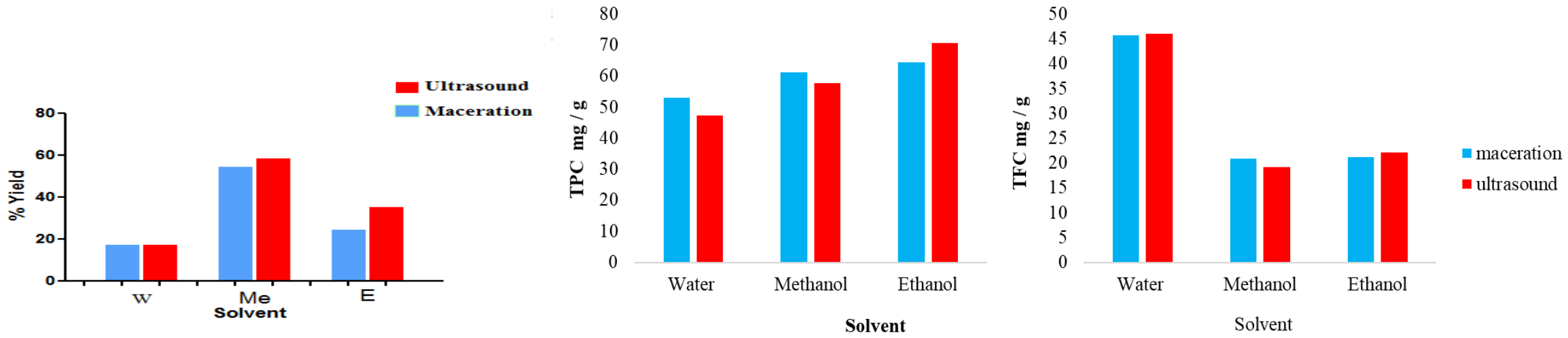
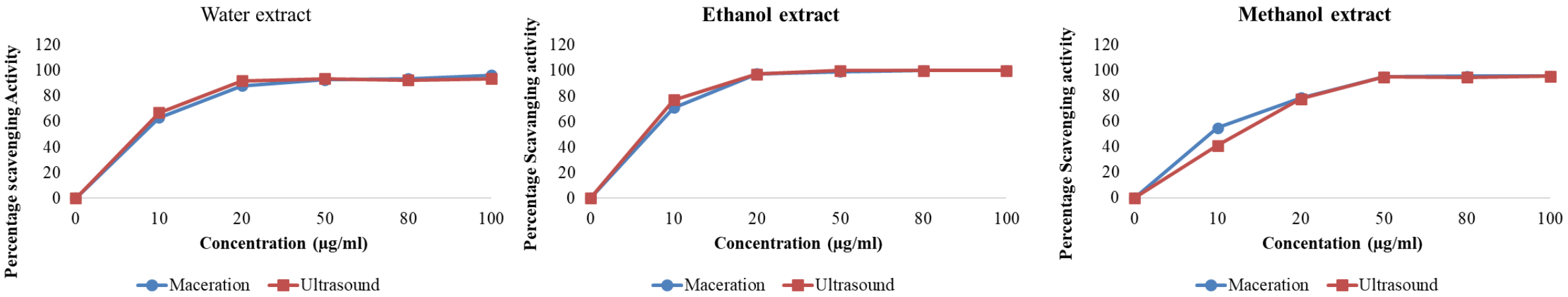
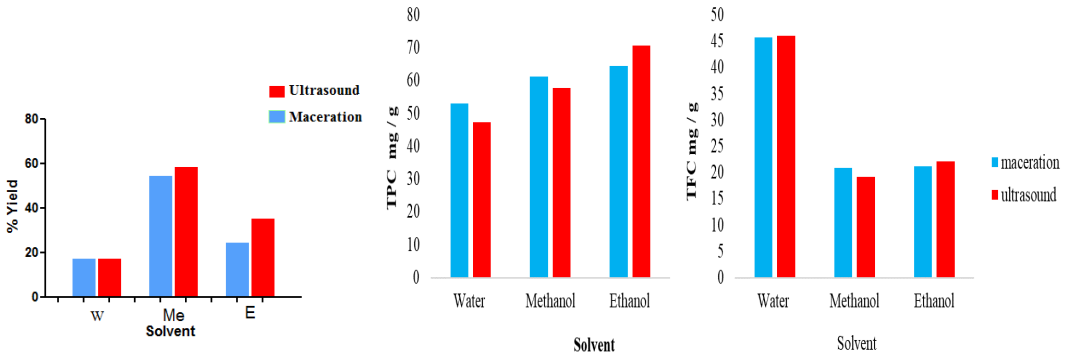


Figure 26. Yield of extraction, Total phenol content (TPC) and total flavonoid content (TFC) from Pomegranate peel of Lebanon using different methods and type of solvents (Unpublished personal data).

Example 3: By-products and wastes from Pomegranate





Extraction method	Ethanol	Methanol	water
Maceration	0.22 µg / ml	0.73 µg / ml	0.2 µg / ml
Ultrasound	0.1 µg / ml	1.07 µg / ml	0.4 µg / ml

IC_{50} values of pomegranate peel extract for the DPPH test.

Figure 27. Antioxidant activity of aqueous, methanol and ethanol extract of the Pomegranate peel obtained by ultrasound and maceration extraction (Unpublished personal data).

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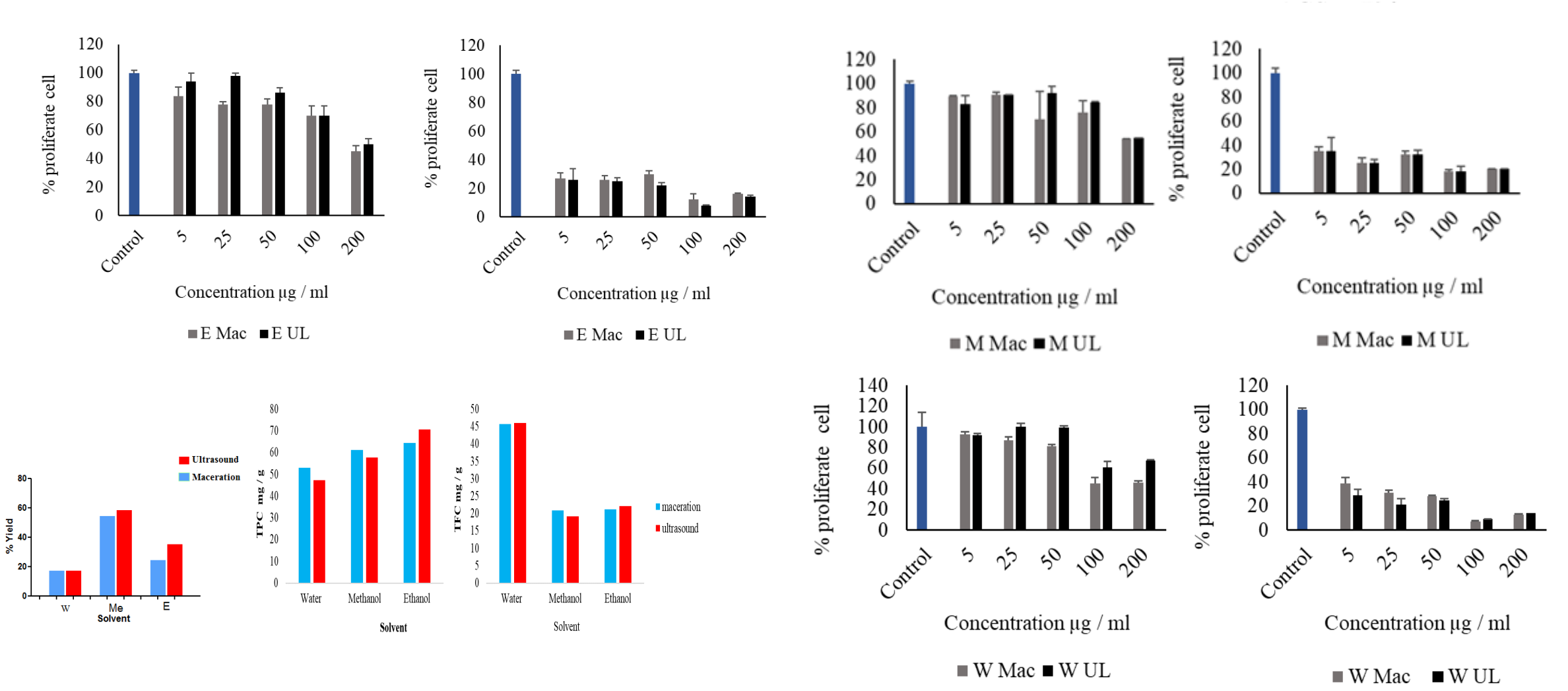
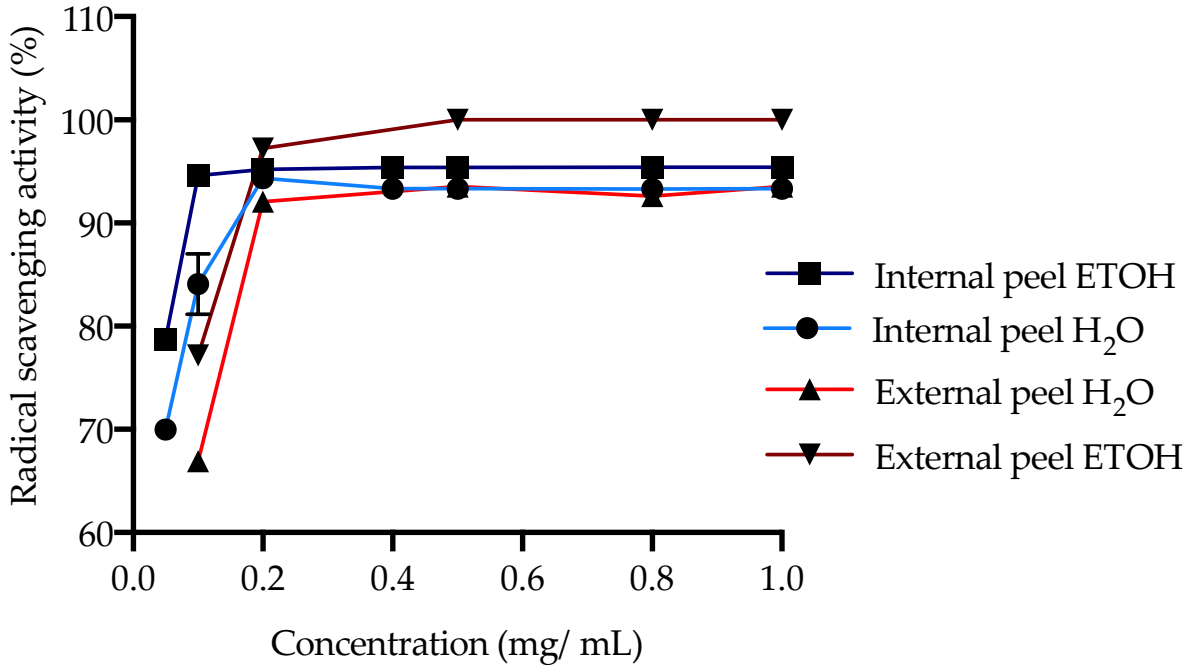


Figure 28. Anti-proliferative activity on human gastric cancer cells of extracts in ethanol (E), methanol (M), or water (W) obtained by ultrasound (UL) and maceration (Mac) (Unpublished personal data)

Example 3: By-products and wastes from Pomegranate

Unpublished personal data obtained in collaboration with Prof Akram Hijazi and his students (Mohamad Ataya, *Houssein Bazzi,* Marwa Fouani) (from Lebanese University, Lebanon) and with Chaker El Kalamouni (from Université de la Réunion, France).



Extract	EC_{50} (mg/mL)
Juice	18.40
Internal peel ETOH	0.36
Internal peel H_2O	0.40
External peel H_2O	0.40
External peel ETOH	0.33

EC_{50} : concentration of extract that reduce 50 % of DPPH activity

Figure 29. Anti-oxidant activity of extracts in ethanol or water obtained by ultrasound from inner and external part of Pomegranate peel (Unpublished personal data)

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Extract	CC_{50} (mg/mL) [a]	IC_{50} (mg/mL) [b]	SI [c]
Juice	> 10	na	na
Internal peel ETOH	1.58	0.35	4.5
Internal peel H_2O	1.60	0.55	2.9
External peel H_2O	1.00	0.35	2.8
External peel ETOH	0.90	0.25	3.6

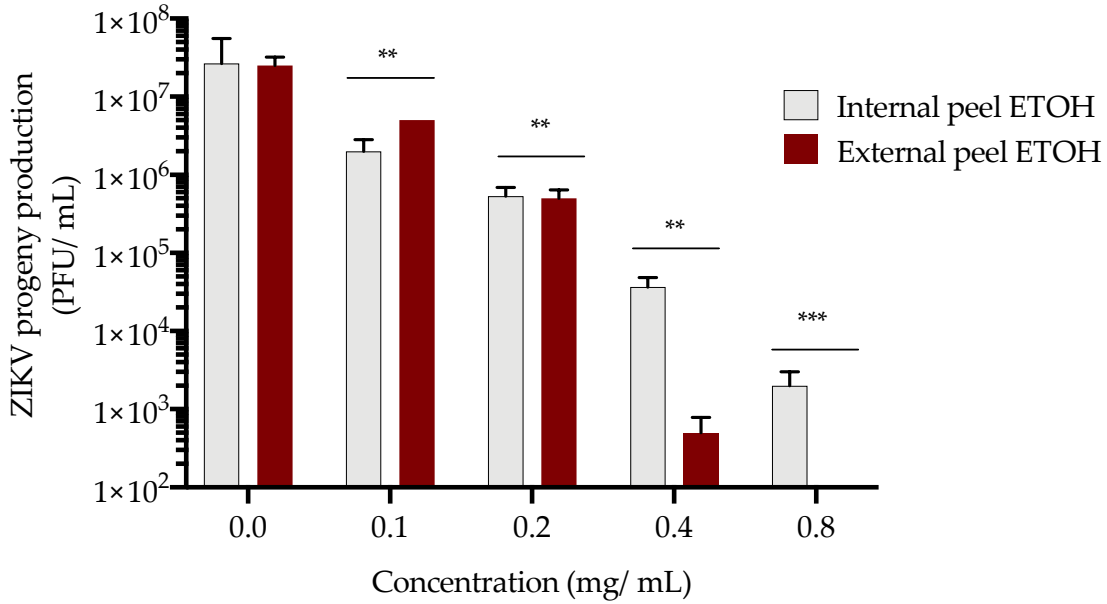

Figure 30. Extracts exhibit dose-dependent antiviral effect against the epidemic strain of Zika virus. Human cells were infected at a MOI of 2 and treated simultaneously with various concentrations of the extract (ranging from 0 to 0.8 mg/mL). The virus growth was evaluated by counting the number of plaques formed. The data is the average of three independent experiments and their standard deviation. The statistical analysis used was one-way ANOVA and Dunnett's test, and the results with ** $p<0.01$ and *** $p<0.001$ were considered as statistically significant. Effect of extracts was measured in term of cytotoxic concentration (CC_{50}) on human cells and inhibitory concentration (IC_{50}) on virus (Unpublished personal data)

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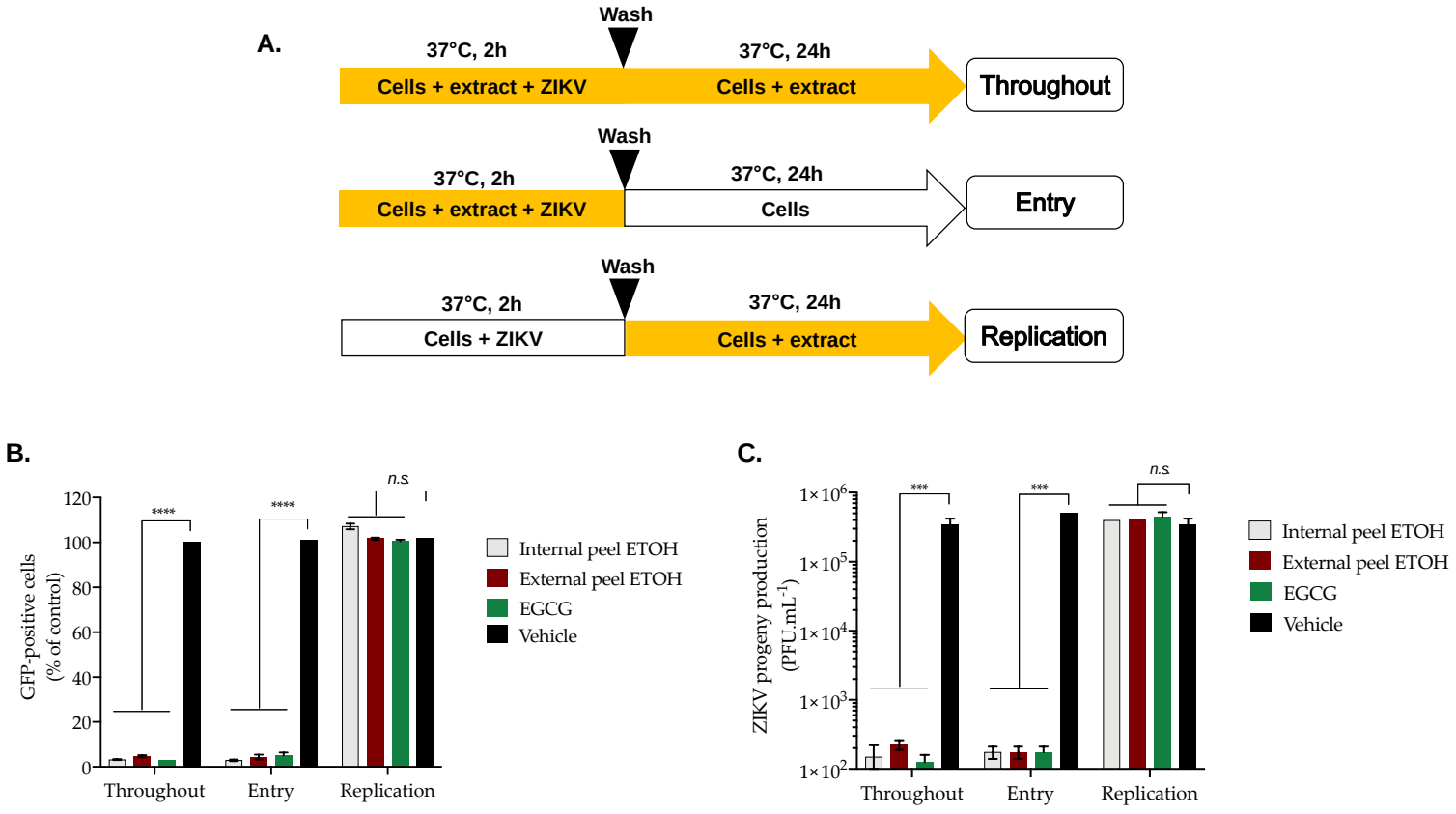

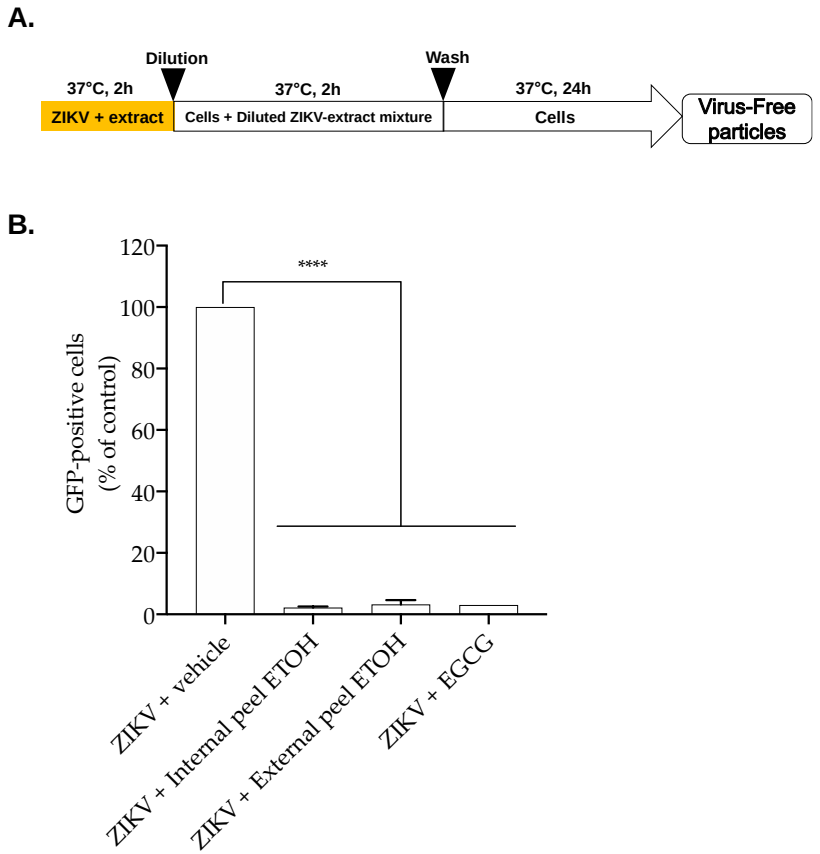

Figure 31. Left image: Extracts inhibit the early stage of ZIKV infectious cycle. **(A)** Representative schematic for time-of-drug addition assay to examine the antiviral activity of extracts. The extracts were added at various points during the infection process, including throughout the entire infection, at the same time as virus entry, and after virus challenge. (B) Flow cytometry was used to analyze the infected cells and (C) measure viral progeny production under the different conditions shown in A. **Right image:** . Extracts preclude virus entry by acting directly on ZIKV particles. **(A)** Schematic representation of virus inactivation assay carried out to characterize the virucidal activity of *P. granatum* extracts. **(B)** ZIKV^{GFP} was incubated with the extracts at a concentration of 0.5 mg/mL for 2 hours at 37°C and subsequently diluted 50 times before infection of cells. EGCG (100 µM) was used as a positive control. The results are means ± SD of three independently performed experiments and are expressed as relative values to untreated infected cells (Unpublished personal data).

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Example 3: By-products and wastes from Pomegranate

Table 4. Utilization and Application of Pomegranate Peel in the Formulation of Value-Added Products

Products	Formulations	Results and Findings
Meat Products		
Goat meatballs	Lean goat meat, PPP, clove essential oil, oregano essential oil, refined vegetable oil, condiment paste, dry spice mix, and refined wheat flour.	Treated samples had considerably higher mean fat values and fiber percentages as compared to control samples.
Chicken meat patties	Chicken meat, sodium chloride, sodium tripolyphosphate, sodium nitrate, spice mix, condiments, breadcrumbs, water, egg liquid, fat, PPP, PPP aqueous extract, pomegranate aril baggage powder, pomegranate aril bagasse powder aqueous extract, and butylated hydroxytoluene.	Compared to pomegranate aril bagasse powder treated samples, PPP had a much higher phenolic content. During refrigerated storage, the TBA value of both control as well as treated patties rose dramatically. Nonetheless, during storage, the TBA values of PPP and aril bagasse powder were considerably lower than those of the control samples. The total plate count and psychrotrophic count of treated samples increase at a slower rate than that of control samples.
Refrigerated meatballs	Beef, breadcrumbs, onion powder, garlic powder, black pepper, cumin, coriander, salt and water, crude PPP, and nano-PPP.	The crude peel's FRAP, total phenolic, flavonoid, scavenging activity, and reducing power increased after being ground. Crude and nano-PPP were added to the meatball, which prevented the development of volatile nitrogen, peroxide, and TBARS, thus preserving the sensory qualities for a cold storage period of 9 days.
Beef burger	Lean meat, fat tissues, sodium chloride, starch, garlic, onion, spice mixture, water, dried PPP.	Moisture content showed a downward trend with increased PPP concentration. Post refrigeration period of 12 days, the protein level of beef burger samples having pomegranate peel concentrations of 2 and 3% was relatively higher, at 14.33 and 14.77%. The considerable difference in TBARS values of samples with 1, 2, and 3% PPP and that of the control sample revealed the beneficial effect of pomegranate peel as a natural antioxidant source.
Refrigerated minced beef meat	Beef, pomegranate peel ethanolic extract, butylated hydroxytoluene, oil.	Samples treated with ethanolic extract of pomegranate peel experienced a considerable reduction in primary as well as secondary oxidation. Ethanolic extract of 1% concentration received the highest scores concerning organoleptic attributes (color, odor, and overall acceptability).
Bakery Products		
Muffin cakes	Wheat flour, egg, sugar, corn oil, milk, PPP, and baking powder.	A significant increase in the total dietary fiber upon substitution with PPP. Control recorded 2.36%, and the PPP substituted sample ranged from 2.80% to 6.48%. Compared to the control muffins, all levels of PPP muffins exhibited significantly greater total phenolic content and antioxidant activity. The drop in the crumb and crust Hunter L and b values increases with the amount of PPP added.
Cakes	Wheat flour, soybean flour, PPP, baking powder, sugar, butter, eggs, and vanilla essence.	The crude fiber and ash content of all types of value-added cakes increased from 2.23 to 3.03% and 1.81 to 2.15%, respectively, as the proportion of PPP substituted increased. The control sample had an overall acceptability of 7.40, that is, liked moderately, whereas the cakes supplemented with wheat, soybean flour, and PPP at levels of 85:10:5, 82.5:10:7.5, and 80:10:10 received the score of 7.80, 7.74, and 7.96, respectively, falling into the "liked very much" classification.

Table 4. Uses of valuable molecules found in Pomegranate peel other than in health (from Singh *et al., ACS Omega,* 2023, 8, 35452−35469, DOI: 10.1021/acsomega.3c02586).

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Table 4. Utilization and Application of Pomegranate Peel in the Formulation of Value-Added Products

Products	Formulations	Results and Findings
Cupcakes	Wheat flour, PPP (5, 10, 15 and 20%), sugar, shortening, fresh egg, milk powder, baking powder.	Cupcakes with 20% supplementation recorded the highest value of ash (1.92%). The highest value for the taste was observed in cupcakes supplemented with 5% PPP. Overall acceptability exhibited a downward trend with regard to the subsequent increase in the concentration of PPP.
Biscuits	Wheat flour, margarine, sugar, salt, baking powder, and PPP.	The values of antioxidant activity, total phenolic content, soluble, insoluble, as well as total dietary fiber were observed as an increase in PPP. The flavor of biscuits made with 18% PPP was more acidic and bitter, which was thought to cause the fall in sensory scores.
Dairy Products		
Curd	Curd, PPE (dried powder), whey protein concentrate, skim milk powder.	With the successive increase in PPE concentration, the overall phenolic content and antioxidant activity of curd increased. However, sensory qualities deteriorated with a further rise in PPE concentration. PPE made curd resistant to microbial count development, pH fluctuations, and whey syneresis during storage period.
Fermented milk beverage	Milk, standard starter culture containing *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*, functional strains, *Lactobacillus plantarum*, and *Bifidobacterium longum* subsp. *longum*, PPE.	The antioxidant activity of the fermented milk beverage FMPO 300 (300 mg/mL) was higher than that of FMPO 150 (150 mg/mL). *In-vivo* research revealed that rats given a functional milk beverage for 30 days showed significantly lower levels of triacylglycerol, LDL cholesterol, and total cholesterol. Also, they had higher HDL cholesterol levels.
Oil Products		
Edible oil	Sunflower, soybean, and corn crude oils, PPE.	Compared to the negative controls (without antioxidant) and the synthetic antioxidant TBHQ-200, in all of the test oils, the pomegranate peel methanolic extract at varying concentration levels showed better antioxidant potential.
Preservatives		
Meat Products	Mutton ribs, spice mixture, condiment mixture, table salt, fat, and pomegranate rind extract.	Even though they were much lower across all storage intervals in the products treated with pomegranate rind extract, the free fatty acid (FFA) levels significantly rose from day 0 to day 21. Over the course of storage, the TPC of the products treated with pomegranate rind extract increased noticeably, and the values were continuously lower than the control. Pomegranate rind extract-treated products significantly outperformed controls regarding appearance and color between the 14th and 21st storage days.

Table 4. Uses of valuable molecules found in Pomegranate peel other than in health (from Singh *et al., ACS Omega,* 2023, 8, 35452−35469, DOI: 10.1021/acsomega.3c02586).

In conclusion

Mediterranean Food Industry By-Products and Wastes

Technology	Key Features	Applications	Advantages
Supercritical Fluid Extraction (SFE)	Uses supercritical CO2 to extract bioactive compounds	Polyphenols, flavonoids, phytochemicals	Environmental friendly, preserves compounds
Microwave-Assisted Extraction (MAE)	Uses microwave energy to heat solvent and plant material	Phenolics, antioxidants	Reduces extraction time and solvent usage
Ultrasound-Assisted Extraction (UAE)	Uses ultrasonic waves to create cavitation bubbles	Lycopene, resveratrol	Low energy consumption, efficient extraction
Enzymatic Hydrolysis	Uses specific enzymes to break down complex molecules	Phenolic acids, flavonoids	Highly selective, preserves bioactive molecules
Pressurized Liquid Extraction (PLE)	Uses high temperatures and pressures to enhance extraction	Carotenoids, polyphenols	High efficiency, scalable for industrial use
Membrane Separation	Uses ultrafiltration and nanofiltration to purify and concentrate compounds	Polyphenols, flavonoids	High selectivity, preserves heat-sensitive molecules
Integrated Extraction Technologies	Combines multiple extraction methods	Various bioactive compounds	Synergistic benefits, optimized recovery

Extracts and pure molecules with

- Antioxidant
- Anti-inflammatory
- Anti-diabetes
- Anti-hypertension
- Anticancer
- Other activities

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