Future Integrative Medicine **2024** vol. 3(2) | 116–131
DOI: 10.14218/FIM.2023.00071

Review Article

Exploring the Molecular Mechanisms and Therapeutic Potentials of Essential Oils: A Systems Biology Approach

Rakesh Kashyap*

Department of Pharmaceutical Sciences, Dr. Harisingh Gour Vishwavidyalaya (A Central University), Sagar, Madhya Pradesh, India

Received: August 30, 2023 | **Revised:** January 16, 2024 | **Accepted:** March 28, 2024 | **Published online:** May 15, 2024

Abstract

Essential oils, known for their pleasant aromas, not only calm the mind and elevate the mood but also captivate the interest of researchers aiming to unveil their vast potential. Various methodologies are employed to explore the diverse capabilities of essential oils, often yielding promising and significant outcomes. This review aims to elucidate the molecular mechanisms of essential oils at the cellular level. It identifies multiple mechanisms through which essential oils exhibit their therapeutic effects across various systems. However, a comprehensive understanding of their fundamental mechanisms still necessitates extensive research. In this review, we discuss the mechanisms underlying the biological activities of essential oils, specifically their antioxidant, antimicrobial, anticarcinogenic, anti-diabetic, and anti-inflammatory properties.

Introduction

Plant's volatile, odorous principles are generally known as essential oils. These are also called ethereal oils. These volatile principles are generally present in secretory structures (like glands, ducts, cavities, and hairs) of plants. Essential oils are found only in 10% of plant kingdoms.[1] Chemically, these oils belong to terpenes, phenols, and nitrogen-bearing compound categories composed of carbon and hydrogen, and other elements found in their molecular structure are oxygen, nitrogen, and sulphur.[2]

Furthermore, essential oils are valuable secondary metabolites of plants, containing various bioactive components that serve multiple functions in plants and possess therapeutic potential. They protect plants from the attack of pathogenic microorganisms and play an influential role in humans for the treatment of chronic diseases and the improvement of various mental health syndromes.[3] Being small and lipophilic, they easily penetrate the skin, exhibit rapid distribution across tissues and organs, and demonstrate swift action. Consequently, essential oils are widely used in traditional remedies for various applications. They possess broad spectrum of biological activities. Recent studies are using system biology to identify and compile the effects and mechanisms of essential oils.[4]

System biology is a unifying approach that connects cells, tissues, and organ systems via molecular components into one system. Interactions among molecular components at the cellular level open a new way to study and evaluate different pathways, diseases, and other characteristics.[5] System biology comprises various biological networks like genetic regulatory, protein interaction, metabolic, and signaling networks. The molecular level is a biological network responsible for chemical interactions and cellular functions in the biological system.[6] It is a broad framework for leading quantitative and inclusive scientific inquiry that facilitates a rigorous investigation of the intricacy of biological systems at all levels of cellular organization.[7] This review aims to identify the potential mechanisms of action of essential oils within systems biology, detailing the various mechanisms through which essential oils exert their effects.

Biological activities of essential oils

Recent studies on essential oils have highlighted their diverse biological activities, including antimicrobial, antiviral, antihelminthic, antioxidant, antiulcer, anti-inflammatory, insecticidal, larvicidal, and immunomodulatory effects. Essential oils find multifaceted applications in the food, perfume, herbal, and cosmetic industries. In the food industry, they are used for flavoring and preservation, while their aromatic properties are exploited in the cosmetic industry as perfumery components.[8,9] The various ways that essential oils work through biological networks to exert their effects and their potential mechanisms of action are described below. (Figs. 1 and 2).

Antioxidative activities of essential oils

The excess of free radicals is responsible for the oxidation process.

Keywords: Essential oil; Antioxidant; Antimicrobial; Anticarcinogenic; Anti-diabetic; Anti-inflammatory.

***Correspondence to**: Rakesh Kashyap, Department of Pharmaceutical Sciences, Dr. Harisingh Gour Vishwavidyalaya (A Central University), Sagar 470003, Madhya Pradesh, India. ORCID: https://orcid.org/0009-0005-3717-8894. Tel: +91-9039 003378, E-mail: rocky24kashyap@gmail.com

How to cite this article: Kashyap R. Exploring the Molecular Mechanisms and Therapeutic Potentials of Essential Oils: A Systems Biology Approach. *Future Integr Med* 2024;3(2):116–131. doi: 10.14218/FIM.2023.00071.

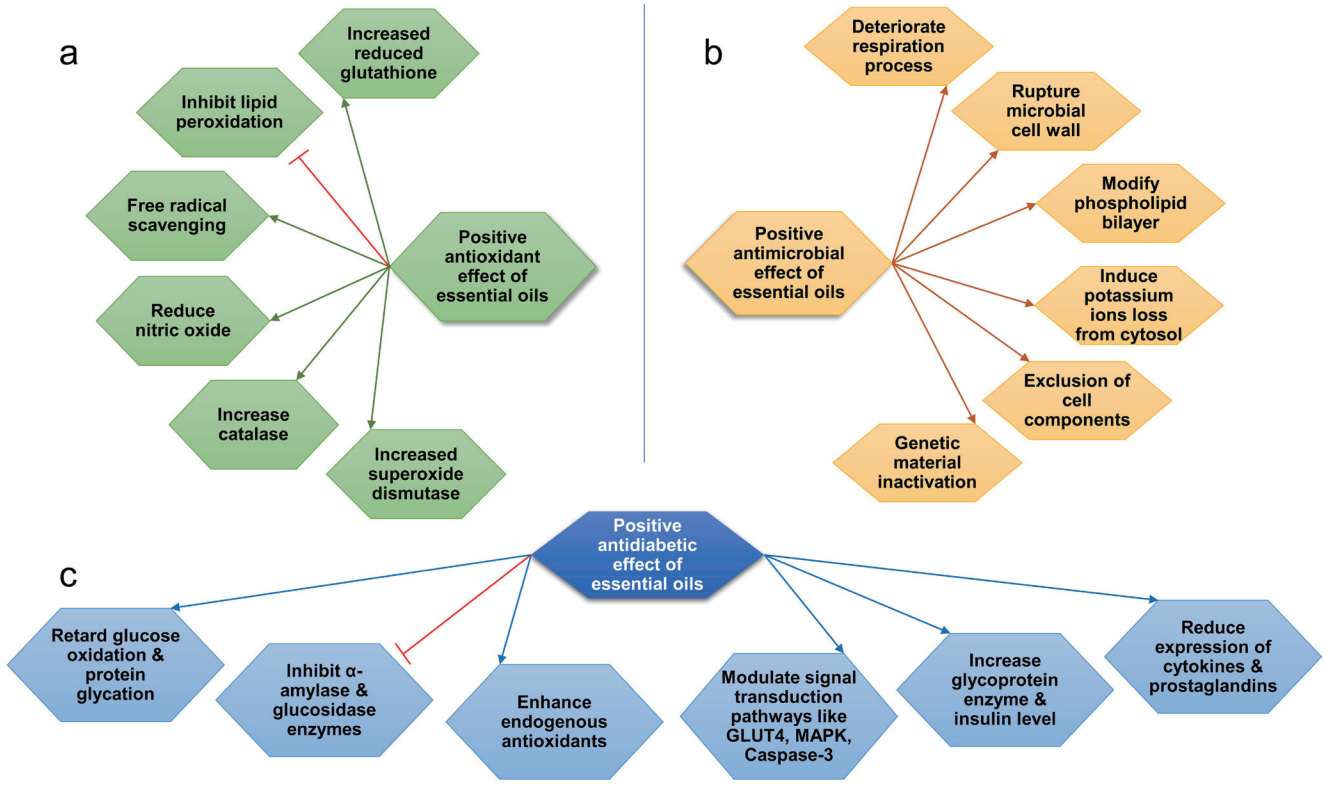

Fig. 1. Mechanism of essential oils to control oxidative stress, microbes and diabetes. (a) Antioxidative mechanism of essential oil. (b) Antimicrobial mechanism of essential oil. (c) Anti-diabetic mechanism of essential oil. GLUT4, glucose transporter protein type-4; MAPK, mitogen-activated protein kinase.

Free radicals induce lipid peroxidation by attacking bio-membranes and start a chain reaction in the human body. As a result, organs and biofilms in the body get harmed in DNA and protein and ultimately cause various diseases like cancer, Alzheimer's, atherosclerosis, and Parkinson's.[10,11] Free radicals generally evolve from external forces like pollution and ultraviolet and internal forces

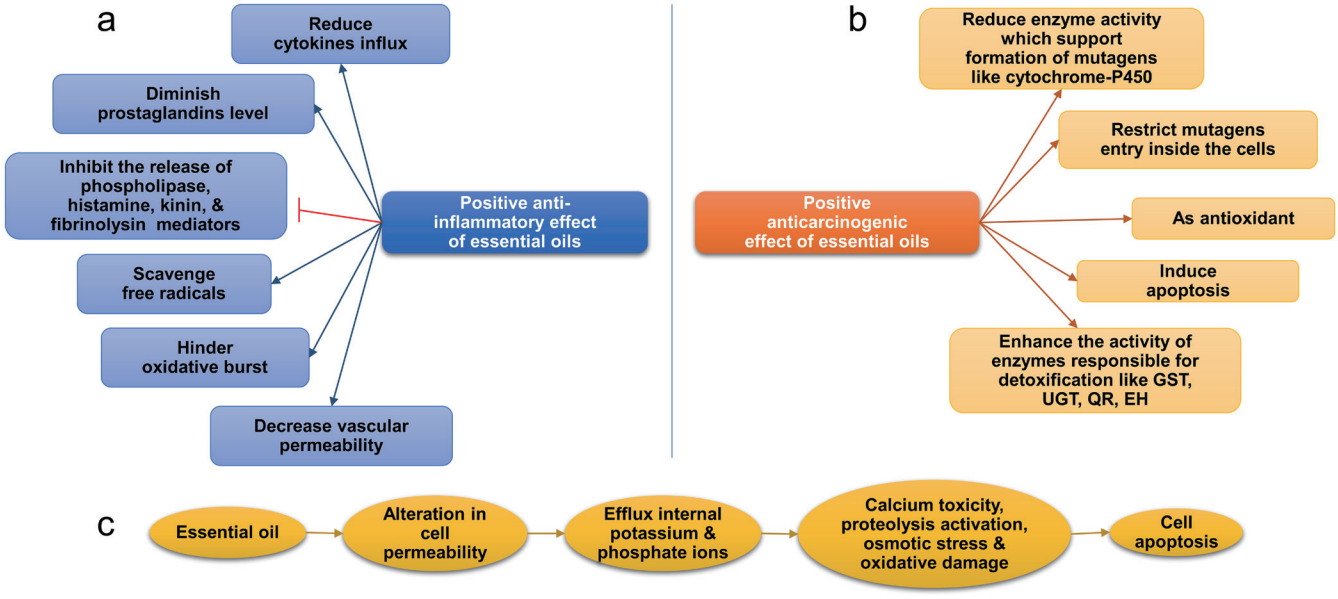

Fig. 2. Role of essential oils in inflammation, cancer, and cell death. (a) Anti-inflammatory mechanism of essential oil. (b) Anticarcinogenic mechanism of essential oil. (c) Mechanism of induction of cell apoptosis by essential oil. EH, epoxide hydrolase; GST, glutathione S-transferase; QR, quinone reductase; UGT, uridine-5'-diphospho-glucuronosyltransferase.

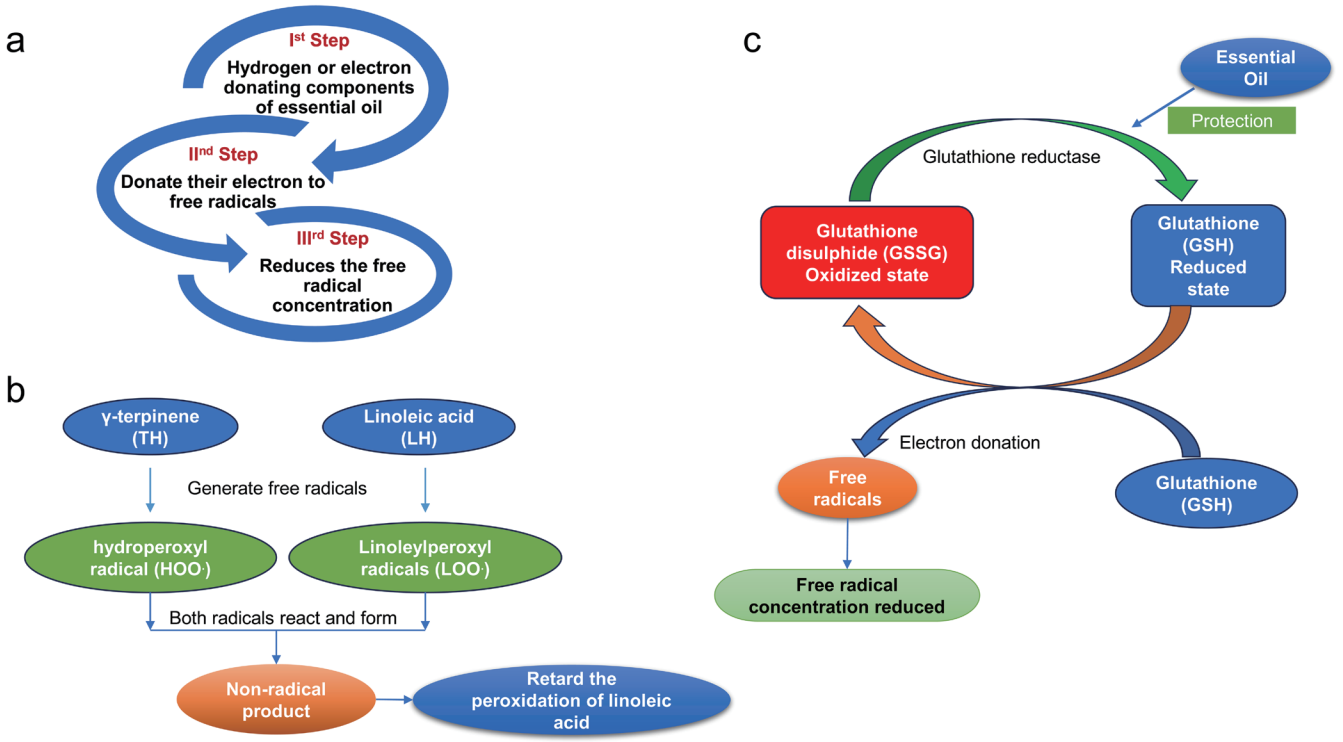

Fig. 3. Antioxidative role of essential oils. (a) Free radical scavenging by essential oils. (b) Lipid peroxidation inhibition by essential oils. (c) Protection of glutathione reductase by essential oil.

like stress and autoxidation. Lipids are essential compounds for the human body, serve as building blocks and energy sources, and are required for various biological functions.[12,13]

There are various *in vitro* approaches for the detection of the antioxidant potential of compounds. Among them Diphenylpicrylhydrazyl (DPPH) assay, β-carotene/linoleic acid assay, chelating effect, and reducing effect are used prominently.

Mechanisms through essential oils exhibit antioxidant potential

In the *in vivo* assessment of the antioxidant effects of compounds, the levels of reduced glutathione, superoxide dismutase, catalase, and nitric oxide are measured. An increase in the levels of reduced glutathione, superoxide dismutase, and catalase, alongside a decrease in nitric oxide levels, indicates a positive antioxidant effect of the compound. This effect is achieved by terminating the chain reactions initiated by free radical intermediates, as these reagents undergo oxidation themselves and prevent further oxidation reactions.[14,15]

Numerous studies have validated the antioxidant potential of essential oils. The analysis of essential oils has confirmed their properties, including hydrogen donating capabilities, free radical scavenging abilities, and the capacity to interrupt the chain reaction of lipid peroxidation,[16] thereby safeguarding healthy cells from damage (Fig. 3).

Mechanism of free radical scavenging action of essential oils

The electron or hydrogen-donating constituent(s) of essential oil donate their electron to free radicals and thus reduce the number of free radicals in the body. The activity is measured with the help of DPPH assay in which antioxidant constituent donates their electron to the DPPH radical. The reaction is confirmed by the change of color of DPPH from colorless to purple/yellow. The concentration is determined by taking its absorption at 519 nm.[17,18]

Mechanism of inhibition of lipid peroxidation by essential oils

A monoterpene hydrocarbon, γ-terpinene, a component of essential oils retards the peroxidation of linoleic acid. During the chain reaction of linoleic acid linoleylperoxyl radicals generated, peroxidation of γ-terpinene yields hydroperoxyl radical. Both free radicals react quickly and form a non-radical product and retard the peroxidation of linoleic acid.[19]

Phenolic components of essential oils donate the phenolic hydrogen atom to free radicals to form resonance-stabilized phenoxyl radicals, which cannot propagate a chain reaction. This inhibits the chain reaction of lipid peroxidation.[20]

In some cases, highly oxidizable components of essential oil get oxidized with the substrate and form peroxyl radicals, which rapidly form non-radical products and decrease the concentration of free radicals.[20]

Mechanism of essential oil on endogenous antioxidants

A Study has demonstrated that essential oils enhance the content of glutathione, a natural antioxidant by protecting the enzyme glutathione reductase.[21] This enzyme is responsible for reducing glutathione disulfide (GSSG) to its sulfhydryl form, known as glutathione (GSH), a potent endogenous antioxidant agent.[22] Glutathione, chemically referred to as γ-L-glutamyl-L-cysteinylglycine, is an eminent endogenous antioxidant, often termed the master antioxidant. It exists in two forms, reduced (GSH) and oxi-

dized (GSSG/GSH disulphide). In its reduced state, the cysteine group of glutathione donates an electron to free radicals, reacts with another glutathione molecule, and forms GSSG. The enzyme glutathione reductase then regenerates glutathione from glutathione disulfide. In a healthy cell, more than 90% of glutathione is present in the reduced state, while less than 10% is found in the oxidized state.[15]

Glutathione protects against toxic metals, alcohol, and organic pollutants. It regulates cell growth and maintains immune function. It reduces mucus and inflammation from the airway during lung detoxification.[23]

Superoxide dismutase stimulates superoxide anions to hydrogen peroxide, which is later converted to water and oxygen by catalase.[24] In mammals, superoxide dismutases (SODs) are found in three isoforms SOD1 (Cu/ZnSOD), SOD2 (MnSOD), and SOD3 (Cu/ZnSOD). These three isoforms SOD1, SOD2, and SOD3 are present in cytoplasm, mitochondria, and extracellularly, respectively.[25] The Superoxide dismutase requires a metallic catalyst for activation and provides defense against superoxide ($O_2^{\bullet-}$) particularly. It is responsible for inhibiting oxidative activation of nitric oxide; thus, it protects endothelial and mitochondrial dysfunction by preventing peroxynitrite formation.[26]

Nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, xanthine oxidase, nitric oxide synthase (NOS), lipoxygenase, and mitochondrial enzymes generate $O_2^{\bullet-}$.[27] The generated superoxide is converted to H_2O_2 by SOD. Dismutation of H_2O_2 by superoxide dismutase produces hydroxyl ($OH^{\bullet}$) free radicles. Superoxide-free radicles and hydroxyl-free radicles act on lipid membranes and encourage the formation of lipid radicle and lipid peroxy radicles, which promote oxidative stress and cause lipid peroxidation.[28] Further, it transformed into water in the presence of catalytic enzymes like glutathione peroxidases (GPx) and peroxiredoxins. Superoxide dismutase is also called first-line defense against superoxide anion radical toxicity because it obstructs the formation of a strong oxidant of peroxynitrite ($ONOO^-$).[29]

Catalase, also known as classical catalases or monofunctional heme catalases, plays a crucial role in detoxifying H_2O_2 by converting it into water and oxygen.[30,31] Studies have shown that it scavenges hydrogen peroxide through a two-step mechanism. In the first step, catalase reacts with hydrogen peroxide in its ferric state, forming a Compound I complex and converting the ferric state to the ferrous state. In the subsequent step, the Compound I complex reacts with another molecule of hydrogen peroxide, forming water and oxygen. Catalase thus facilitates the removal of hydrogen peroxides, which are generated in red blood cells and protects pancreatic β-cells from the damaging effects of hydrogen peroxide.[32,33]

Excess and unregulated nitric oxide production injures cell proteins and alters their functions. Its deficiency is responsible for the dysfunction of the endothelial system.[34]

Nitric oxide is produced from L-arginine and oxygen in the presence of cofactors, including tetrahydrobiopterin (BH_4), by NOS. Along with nitric acid, citrulline is also generated by the reaction. Nitric oxide further oxidized in blood and tissues, leading to nitrite and nitrate formation, which have a half-life of 2 min and 6 h, respectively. Nitric oxide reduces mitochondrial respiration and affects energy production by interacting with cytochrome c oxidase.[35]

Electron from NADPH flows from the reductase sphere to the oxidative sphere of NOS (Nitric oxide synthase). NOS is a heme-containing enzyme with oxidative and reductase spheres linked via calmodulin. Electron transfer requires two cofactors, flavin adenine dinucleotide and flavin mononucleotide. Electrons finally reach the reduced heme iron of NOS's oxidative domain, permitting binding of oxygen molecules and initiating nitric oxide generation.[36]

The mechanism of oxidation by nitric oxide is not known. However, it is fictional that it induces apoptosis by interacting with amino acid receptors, depleting cellular NAD^+, and activating caspases. Nitric oxide regulates transcription factors or disperses in blood by binding with the heme portion of cytochrome c oxidase in mitochondria. In the vascular lumen, nitric oxide binds with ferrous heme, forming methemoglobin and nitrate.[37] In smooth muscle cells, essential oils modulate the activity of heme-containing guanylyl cyclase enzyme. Guanylyl cyclase is responsible for synthesizing cyclic guanosine 3′,5′-cyclic monophosphate from guanosine triphosphate through dephosphorylation. This synthesis, in turn, activates potassium channels and inhibits calcium channels. The inhibition of calcium channels leads to the phosphorylation of the myosin chain and sarcoplasmic proteins by activating protein kinase. This process promotes the sequestration of calcium ions in the sarcoplasmic reticulum while reducing their concentration in the cytosol, which impacts phosphorylation and consequently results in smooth muscle relaxation (Fig. 4).[38]

Works that reflect the antioxidant activity of essential oils

Essential oil from the stem of *Eugenia caryophylata* showed a higher scavenging effect at 0.82 ± 0.15 µg/mL as compared to essential oil obtained from bud and leaf at the dose of 1.18 ± 0.56 µg/mL and 1.16 ± 0.74 µg/mL respectively.[39] The essential oil of *Croton campinarensis* exhibited 1.88 ± 0.08 $mM \cdot L^{-1}$ the Trolox Equivalent Antioxidant Capacity in the DPPH assay. It is almost double the standard Trolox.[40]

Essential oils of *Anethum graveolens* and *Thymus daenensis* exhibited higher lipid peroxidation inhibitory effects than synthetic standard compounds. Essential oil of *Anethum graveolens* showed a higher half-maximal inhibitory concentration (IC_{50}) superoxide radical scavenging effect than essential oil of *Thymus daenensis* at the dose of 0.001 and 0.013 mg. The essential oil of *Anethum graveolens* and *Thymus daenensis* showed (IC_{50}) nitric oxide radical scavenging effect at the dose of 0.0014 and 0.005 mg.[41]

In vivo assessment of *Artemisia visnaga* essential oil proved an increase in the activity of catalase, superoxide dismutase, and plasma glutathione peroxidase.[42] *Origanum rotundifolium* Boiss essential oil was found to have an effective radical scavenging effect and inhibitory effect on lipid peroxidation at the dose of 15.30% ± 0.64 $mg \cdot mL^{-1}$ and 34.46% ± 1.82 $mg \cdot mL^{-1}$ respectively.[43]

Amiri worked on *Thymus daenensis* (*lancifolius*) Celak and *Thymus eriocalyx*. He found better scavenging effect of *Thymus daenensis* (*lancifolius*) Celak at the dose of 19.1 ± 0.1 µg/mL and better inhibitory lipid peroxidation effect of *Thymus eriocalyx* at the dose of 34.2 ± 0.4 µg/mL.[44] *Salviae aetheroleum* (Sage) replicates a good radical scavenging effect with 10.5 µL/mL and effective inhibition of 15-lipoxygenase (responsible for the generation of lipid peroxides via oxidation of unsaturated fatty acids) at 0.064 µL/mL.[45]

Carvacrol isolated from the *Nigella sativa* L. essential oil reflects prominent radical scavenging action. It has also been found to have protective effects against lipid peroxidation.[46] *Syzygium aromaticum*,[47] *Nepeta ciliaris,* and *Nepeta leucophylla* showed good radical scavenging effects at 5.76 $\mu g \cdot mL^{-1}$, 0.9 ± 0.2 mg/mL, and 1.2 ± 0.5 mg/mL, respectively. *Erigeron mucronatusi, Erigeron annuus,* and *Nepeta leucophylla* showed better inhibitory effects on lipid peroxidation.[48]

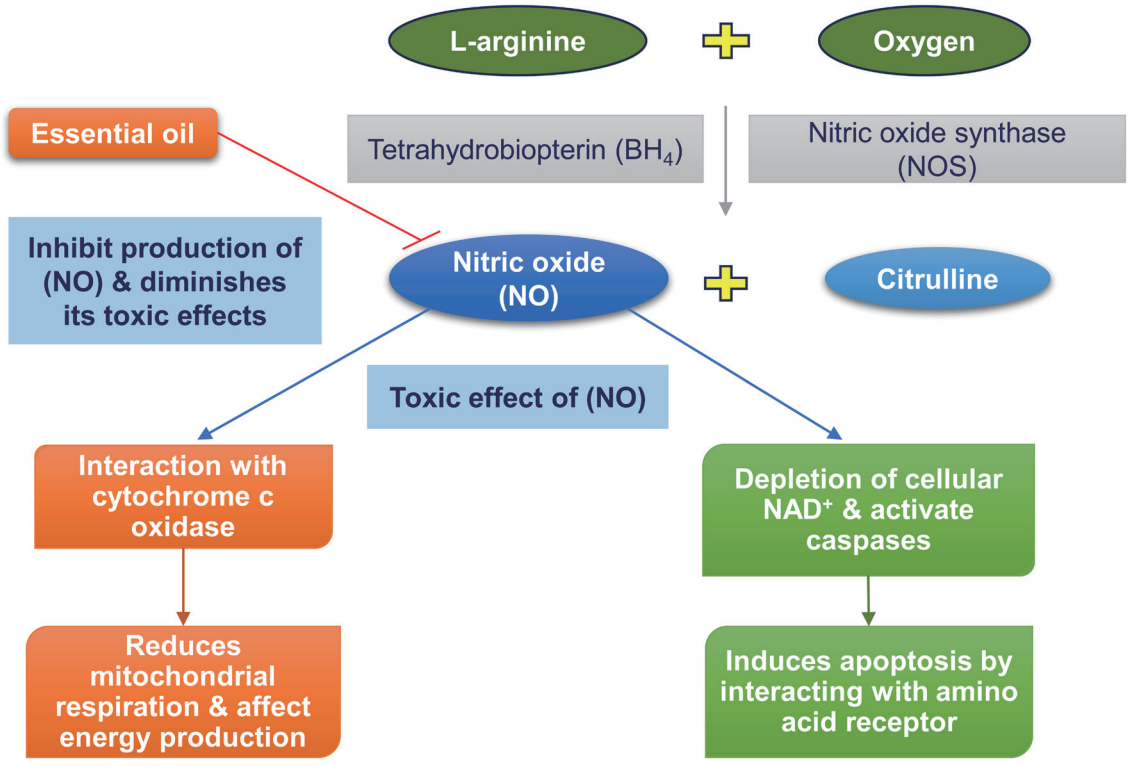

Fig. 4. Function of nitric oxide and role of essential oil.

The effective free radical scavenging effect is also shown by *Origanum campactumi*, *Curcuma zedoaria* Rosc, *Eucalyptus camaldulensis* and *Phoenix dactylifera*.[49–51] Ozkan *et al*.[52] worked on *Salvia pisidica* essential oil and found its better effect on scavenging of free radical and hydroxy radical and inhibition of linoleic acid.

Antimicrobial role of essential oils

Essential oils have demonstrated potential as antimicrobial agents, with research uncovering various mechanisms of action against microbes. The antimicrobial effects of essential oils are manifested through the following mechanisms: a) rupturing the microbial cell wall or altering the phospholipid bilayer, leading to the expulsion of cell components; b) increasing the loss of potassium ions from the cytosol; c) deactivating or destroying genetic material; d) impeding the respiration process; and e) weakening enzyme systems involved in synthesis.

Antibacterial mechanism of action of essential oils

Studies have shown that essential oils increase the permeability of the bacterial cell membrane, which results in the leakage of intracellular components and the uptake of extracellular macromolecular substances.[53] This disrupts the cell wall structure and causes the microbial cells to shrink.[54] Changes in membrane permeability lead to the efflux of internal potassium and phosphate ions. A high concentration of extracellular potassium ions can cause severe and irreversible damage to the cytoplasmic membrane. Phosphate, a major component of adenosine phosphates (mono, di, and triphosphates), DNA (deoxyribonucleic acid), and RNA (ribonucleic acid), is typically released by hydrolysis. This release can destroy structures and interrupt the synthesis of specific macromolecules, such as DNA and RNA.[55] It also inhibits the activity of the enzyme ATPase and modifies the growth of bacteria. A study on the essential oil of *Cupressus funebrisi* revealed the exclusion of bacterial protein by rupturing the cell wall, which is responsible for the maintenance of the integrity of the cell.[56]

Disruption in cell membrane permeability results in extensive dyshomeostasis (imbalance of homeostasis). Calcium toxicity, proteolysis activation, osmotic stress, and oxidative damage are the results of alteration in homeostasis, ultimately leading to cell death.[57] Efflux of potassium alters the conductivity of the cell and leads to the loss of potassium ions along with water, resulting in shrinkage of the cell and leading to the apoptosis of the cell.[58,59]

Works that reflect the antimicrobial activity of essential oils

Essential oil of *Origanum vulgare* L found strong antimicrobial action against *Staphylococcus aureus*, *Enterococcus faecium* and, *Escherichia coli* isolates when tested for minimum inhibitory concentration, ranging from 0.29 to 1.15 mg/mL probably due to distraction of bacterial cytoplasmic membrane structure and function.[60] Essential oils of *Origanum compactum* give a positive response for the cell permeability alteration and integrity when tested for leakage of cellular components against *Escherichia coli* and *Bacillus subtilis*.[61]

Crude essential oils of lemongrass, palm rosa, and eucalyptus showed higher leakage of bacterial cellular material than the individual major components (citral, geraniol, and citronellal) of essential oils when tested against *Staphylococcus aureus* and *Escherichia coli*. The essential oil and its components have been observed to increase the concentration of extracellular potassium ions compared to the control. This effect is likely due to the oils' ability to disrupt the permeability barrier of microbial membranes.[62]

The *in vitro* antibacterial activity of the leaf essential oil from *Forsythia koreana* demonstrated potent antibacterial effects against foodborne pathogenic bacteria. At a concentration of 5 mL/disc, the inhibition zone diameters measured 12.3 mm for *Salmonella enteritidis* KCTC 12243, 8.0 mm for *Escherichia coli* ATCC 8739, and 9.3 mm for *Staphylococcus aureus* ATCC 6538.

The essential oil diminishes the cell integrity, increases permeability, and distorts membrane permeability.[63]

Estragole, isoeugenol, and eugenol, the phenylpropene constituents of essential oil, inhibited enzymatic activity up to 50%, 90%, and 88%, respectively, at the concentration of 30 milimolar.[64] *Monarda didyma* essential oil reduces the activity of glucose-6-phosphate dehydrogenase, citrate synthase, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase in Carbapenem-resistant *Klebsiella pneumoniae*. It also inhibits biofilm formation, damages cell membrane structure, and inhibits energy metabolism.[65]

Anticarcinogenic role of essential oils

Cancer is a non-communicable and multifactorial disease that has unmanageable growth and abnormal mechanisms of cell division. In various studies, natural compounds showed promising chemotherapeutic properties.[66,67] Cancer can be categorized into three distinct stages. In the first stage, a carcinogen causes a mutation in the cell and damages the genetic materials. The second stage is identified with unconditional cell growth, deformation of tissue structure, and inflammation. In the third stage, cells form tumors by unlimited cell growth and modification in gene expression.[68]

Natural compounds are an important part of several clinically useful anti-cancer agents. Vincristine, vinblastine, camptothecin derivatives, etoposide, and paclitaxel are effective and established anti-cancer compounds.[69]

Anticarcinogenic mechanism of essential oil

Essential oils or their components work as antimutagenic compounds by a) constraining mutagens entry inside the cell and b) decreasing enzyme activity, which supports the formation of mutagens like cytochrome-P_{450}.[70,71] They act as a detoxifying agent via enhancing the activity of enzymes responsible for detoxification like glutathione S-transferase (GST),[72] uridine-5′-diphosphoglucuronosyltransferase, quinone reductase (QR) and epoxide hydrolase.[73–75] It worked as an antioxidant agent by protecting the oxidative impairment of cells through increasing endogenous antioxidant enzymes like GSH, SOD, catalase, and GPx.[14] It also acts as an anti-proliferative agent and indices apoptosis by a) changing the mitochondrial membrane barrier, b) increasing reactive oxygen species, c) decreasing internal glutathione level[76,77] d) increasing cytochrome-C activity, e) disturbing B-cell lymphoma-2 and B-cell lymphoma-2-associated X protein (Bcl/Bax) proportion, f) increasing caspase 3 and caspase 9 action, and g) poly ADP ribose polymerase.[78–80]

Mutagens are substances that cause DNA damage, affecting DNA replication and leading to mutagenesis through three main processes: a) reduction in replication fidelity, characterized by incorrect nucleotide incorporation; b) frameshift mutations, which involve disturbances in the DNA sequence due to the addition or subtraction of nucleotides in the newly synthesized DNA strand; and c) replication hindrance, where incorporation points in DNA are blocked.[81]

Cytochrome P450 represents a large family of enzymes responsible for catalyzing various oxidation-reduction reactions, present in all mammalian tissues, with the most reactive forms found in the liver, kidney, and small intestine.[82] These enzymes act as metabolic activators for many procarcinogens, converting them into carcinogens. The further oxidative activation of carcinogens leads to the development of electrophilic reactive intermediates, which bind to DNA and cause mutation.[83]

Detoxifying enzymes play a crucial role in converting toxic metabolites into less toxic and harmless compounds, facilitating their excretion from the body. This process, known as biotransformation or detoxification, is divided into two phases: Phase I and Phase II.

Phase I reactions are non-synthetic reactions, including oxidation, reduction, and hydrolysis. The site of phase I is the liver. Phase II reactions are biosynthetic or conjugation reactions.[84] GSTs are a phase II enzyme of biotransformation reaction. A group of eight dimeric enzymes maintains cell homeostasis and catalyzes the conjugation reaction of reduced glutathione. It catalyzes the metabolism of electrophiles generated from cytochrome P450 and converted to glutathione conjugates, which can be readily excreted outside the body.[85,86] In some cases, these glutathione conjugates get more reactive and form episulfonium intermediates, which are responsible for DNA modification.[87] For detoxification reaction, intracellular and extracellular control of the homeostatic environment is required. It is achieved by maintaining the GSH/GSSG ratio. The glutathione conjugate converts lipophilic compounds into more readily eliminated water-soluble metabolites.[88]

Uridine diphosphate-glucuronosyltransferases are responsible for converting many exogenous, endogenous lipophilic compounds and xenobiotics into more polar substances so that they can be readily excreted from the body through bile and urine.[89] It is an important enzyme of glucuronidation (detoxification mechanism of the body),[90] responsible for the biotransformation of carcinogens that enter into the body through diet or as pollutants from the air. In the bladder, acidic urine is responsible for the hydrolysis of glucuronide-carcinogen to release ultimate carcinogens.[91,92]

QR plays a pivotal role in the detoxification process by reducing electrophilic quinones. In cancerous cells, QR can activate certain chemotherapeutic agents, such as mitomycins and aziridylbenzoquinones, promoting the death of cancer cells.[93] Epoxide hydrolase is instrumental in inactivating epoxide genotoxic intermediates, thereby protecting the body from epoxide toxicity. It operates by binding with the substrate to form enzyme-substrate ester intermediates, which are subsequently hydrolyzed by an activated water molecule (Figs. 5 and 6).[94]

Works that reflect the anticarcinogenic activity of essential oils

Essential oils of *Citrus sinensis* and *Citrus latifolia*, both prove their antimutagenic ability by reducing alkylated DNA damages through a reduction in the expression of base-substitution mutations and by reducing the activation of pre-mutagens like 2AA.[95] Monoterpenes found in sage and sage oil have been identified as antimutagenic against UV-induced mutations. Studies have shown that essential oil reduces mitomycin C-induced chromosome aberrations in mice, demonstrating its chemoprotective properties.[96] Additionally, essential oil and two compounds, 1,8-cineole and geraniol, from *Amomum tsao-ko* were tested on a series of human cell lines and found to be particularly effective against human liver carcinoma cell lines (HepG2), with an IC_{50} value of 31.80 ± 1.18 μg/mL. Essential oil proved to be more effective compared to its individual components and also increased the percutaneous permeation rate. Cytotoxic studies have confirmed the cytotoxic effect of the essential oil.[97]

Boswellia sacra essential oil was tested for three human breast cancer cell lines (T47D, MCF7 and MDA MB-231) and avoids

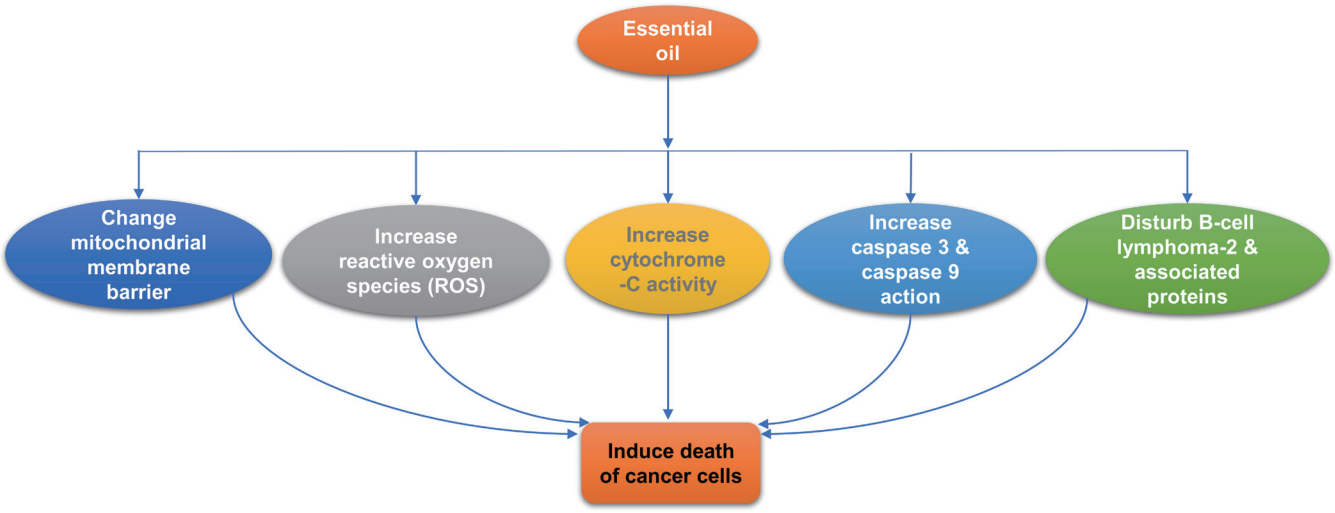

Fig. 5. Mechanism of induction of cancer cells death by essential oils.

cellular network formation, induces cancer cell death and cessation of multicellular tumor spheroids.[98] *Casearia sylvestris* essential oil showed a selective cytotoxic effect against human cervix carcinoma cell line (HeLa), human lung cancer cells (A-549), and human colon adenocarcinoma cells (HT-29) at 63.3, 60.7 and 90.6 µg/mL respectively.[99] *Commiphora gileadensis* essential oil exhibited anti-proliferative and proapoptotic effects through DNA "ladder" and caspase-3 activation in cancer cell lines.[100] *Thymus fallax* essential oil decreases cell index values in a concentration dependent manner when tested against colorectal cancer cells (DLD-1). 50% inhibitory concentration was found at 0.347 mg/mL.[101]

Rosmarinus officinalis essential oil exhibited dose-dependent cytotoxicity (inhibition of cell proliferation) against human breast adenocarcinoma (MDA-MB-231) cells with IC_{50} value at 59.35 µg/mL.[102] *Citrus aurantifolia* essential oil tested against colon cancer cells (SW-480) at 100 µg/mL and showed effectivity through DNA fragmentation and induction of caspase-3.[103]

Ocimum basilicum essential oil found good anticarcinogenic

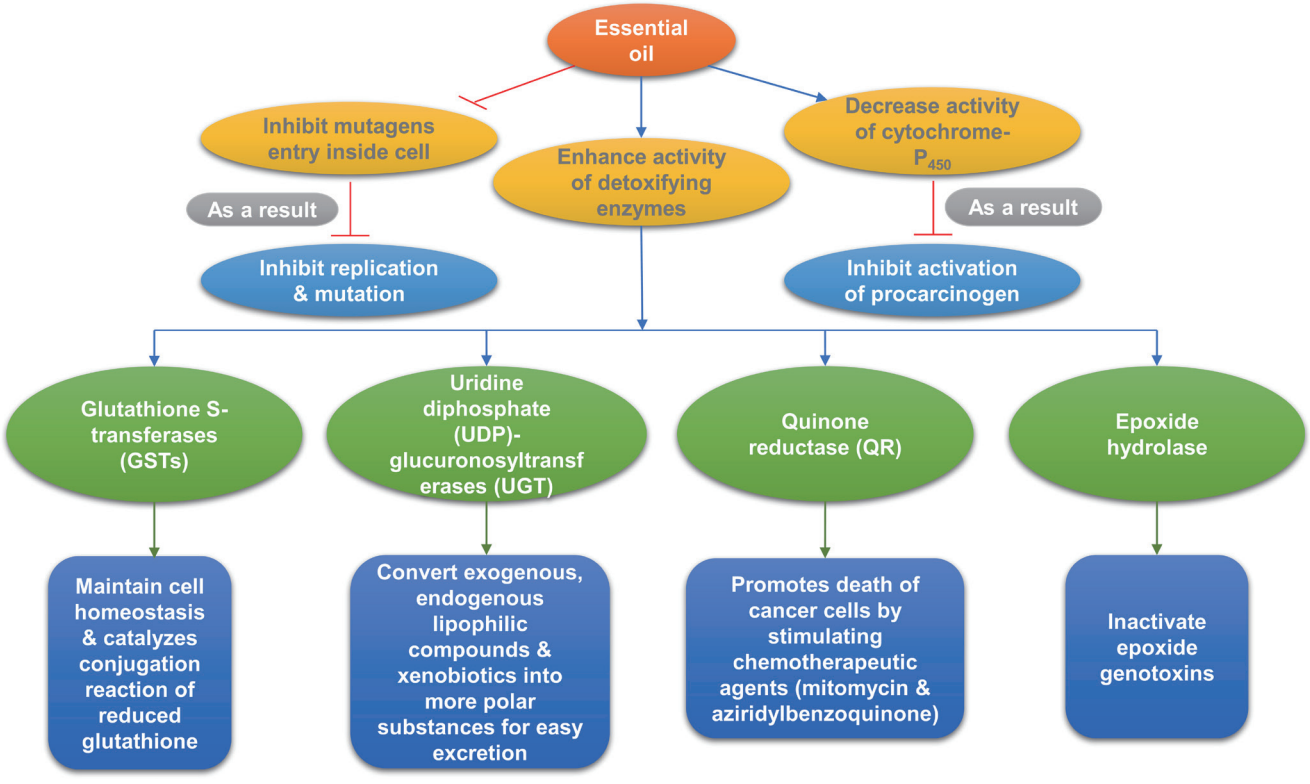

Fig. 6. Antimutagenic and detoxifying mechanism of essential oil.

activity against human liver adenocarcinoma cell lines (Hep3B) at 56.23 ± 1.32 µg/mL and human breast cancer cell lines (MCF-7) at 80.35 ± 1.17 µg/mL.[104] Essential oil of *Zingiber ottensii* plants showed 50% minimum inhibitory activity against human lung cancer cells (A-549) at 43.37 ± 6.69 µg/mL, human breast cancer cell lines (MCF-7) at 9.77 ± 1.61 µg/mL, human cervix carcinoma cell line (HeLa) at 23.25 ± 7.73 µg/mL and myelogenous leukemia cell lines (K562) at 60.49 ± 9.41 µg/mL.[105]

Nepeta mahanensis essential oil showed significant cytotoxic activity against MCF-7 (breast cancer cell lines), Caco-2 (human colorectal adenocarcinoma cell lines), SH-SY5Y (human Neuroblastoma cell line), and HepG2 (human liver carcinoma cell lines) cancer cell lines. Its cytotoxic effect was due to the necrosis/apoptosis-inducing action.[106]

Anti-diabetic role of essential oils

Upon uptake, glucose is phosphorylated to glucose-6-phosphate in the presence of the glucokinase enzyme. Its subsequent metabolism generates ATP, which then inhibits ATP-sensitive potassium channels. The inhibition of these potassium channels leads to the opening of voltage-dependent calcium channels (L-type), resulting in an increase in intracellular calcium ions, which triggers the release of insulin.[107]

Additionally, two components, glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, further enhance the pancreatic cells' ability to secrete insulin. Both components are released in the intestine following the ingestion of food and are short-lived, being deactivated by the enzyme dipeptidyl peptidase-4.[108–110]

A high-fat diet stimulates mitochondrial proteins and transcription factors that cause inflammation and dysfunction of adipose tissues. The changes induce the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukins (IL-6 and IL-1β), known as metabolic inflammation, which plays a significant part in insulin-resistant and type-2-diabetes mellitus subsequently.[111,112]

Anti-diabetic mechanism of essential oil

As anti-diabetic, essential oils generally scavenge the free radicals and retard glucose oxidation and protein glycation as well.[113] Essential oils modulate various signal transduction pathways linked to glucose metabolism, such as mitogen-activated protein kinase (MAPK), glucose transporter protein type-4 (GLUT4), Caspase-3, etc.[114] They significantly reduce the expression of TNF-α, IL-1β, IL-4, IL-6, iNOS and cyclooxygenase 2 (COX-2).[115,116] Essential oils increase insulin levels, glycoprotein enzymes, enhance endogenous antioxidant enzymes like SOD, catalase, and GPx, reduce glutathione and vital glycolytic enzymes.[117] Essential oils inhibit α-amylase and glucosidase enzymes, which catalyze carbohydrate metabolism, thus retard glucose release and absorption and, in turn, suppress postprandial hyperglycemia.[118,119]

MAPK activity encompasses extracellular-signal-regulated kinases (ERKs), jun amino-terminal kinases (JNKs), and p38/SAPKs (stress-activated protein kinases). Research indicates that inhibiting or modulating the activity of p38 MAPK and JNKs can restore the function of aquaporin 7 (AQP7), a member of the aquaporin family. This restoration leads to an increased influx of glycerol, thereby stimulating insulin secretion.[120,121] Caspase 3 activity plays a crucial role in β-cell apoptosis, which reduces insulin production. Altering or diminishing caspase 3 effects can decrease β-cell apoptosis and maintain insulin levels.[122,123] Upon the signal of insulin, GLUT4 translocated from intracellular vesicles to the plasma membrane to enhance glucose metabolism and reverts to intracellular vesicles once glucose levels normalize.[124,125]

Hepatic PGF2α (prostaglandin F 2α) induces insulin resistance. It binds to the FP receptor in the liver, increases the activity of enzyme phosphoenol-pyruvate carboxykinase (PCK1) and glucose-6-phosphatase (G6Pase), and increases the process of gluconeogenesis. COX-2 and PGI_2 (Prostagaldin I 2/Prostacyclin) also induce gluconeogenesis and induces insulin resistance.[126] Insulin resistance induces lipolysis and decreases intracellular triglyceride storage. It reduces fat content and increases the release of non-esterified fatty acids, which deposit fat from adipose tissue into the liver and muscles. Furthermore, adipose insulin resistance facilitates the release of adipokines (such as adiponectin, leptin, and resistin) and cytokines (like TNF-α, IL-6 and IL-1β) leading to chronic inflammation and hyperglycemia. Thus, inhibition of prostaglandins and cytokines retards insulin resistance, enhances glycoprotein enzymes, and raises insulin levels.[127]

α-amylase (salivary and pancreatic) transformed carbohydrates into glucose.[128] It hydrolyzes the glycosidic bond of polysaccharides and converts them into oligosaccharides and further into simple sugars.[129] Glucosidase (intestinal) converted disaccharides into glucose. Inhibition of both enzymes delayed glucose absorption and its transportation into the blood.[130]

Deactivation of AMP-activated protein kinase (AMPK) impairs the function of GLUT4, whereas its activation enhances GLUT4 expression. Activation of AMPK prevents the polarization of pro-inflammatory macrophages (M1) triggered by lipopolysaccharide, thereby reducing inflammation and subsequently improving insulin resistance. Furthermore, AMPK activation boosts glucose utilization in peripheral tissues by inhibiting liver gluconeogenesis, supporting metabolic balance and glucose homeostasis (Figs. 7 and 8).[131]

Works that reflect the anti-diabetic activity of essential oils

The histological and other studies proved that the essential oil of *Pelargonium graveolens* at the dose of 150 mg/kg body weight in alloxan-induced diabetic rats gives better results than glibenclamide. The study suggests that it worked by improving glucose, persuading insulin release, and peripheral acceptance of glucose. It decreases blood glucose and increases hepatic glycogen.[132] Intraperitoneal administration of the *Citrus sinensis* essential oil in alloxan-induced diabetic rats significantly reduces fasting blood glucose and hepatic glucose and increases hepatic glycogen at 110 mg/kg body weight. It is supposed that the effect was due to the presence of monoterpenes, which have insulin-mimetic properties, potentiate insulin secretion, and enhance glucose uptake from the blood.[133]

Essential oils of *Salvia officinalis* and *Mentha suaveolens* showed inhibitory effects on α-amylase and α-glucosidase. α-amylase inhibition was obtained at 81.91 ± 0.03 µg/mL (IC_{50} value) and 94.30 ± 0.06 µg/mL (IC_{50} value), and α-glucosidase inhibition was obtained at 113.17 ± 0.02 µg/mL (IC_{50} value) and 141.16 ± 0.2 µg/mL (IC_{50} value) by *Salvia officinalis* and *Mentha suaveolens* respectively.[134] *Coriandrum sativum* L. essential oil showed a protective effect on kidney and pancreatic cells in histological studies in streptozotocin-induced diabetic rats. By protecting the β-cells, it improves insulin secretion and helps to reduce blood glucose levels.[135] *Myrtus nivellei*'s essential oil findings showed its hypoglycemic potential when it was tested for streptozotocin-induced diabetic rats. It significantly decreases blood sugar and triglyceride levels.[136]

Clove essential oil has demonstrated a significant anti-diabetic effect by reducing blood glucose levels and acting on glucose met-

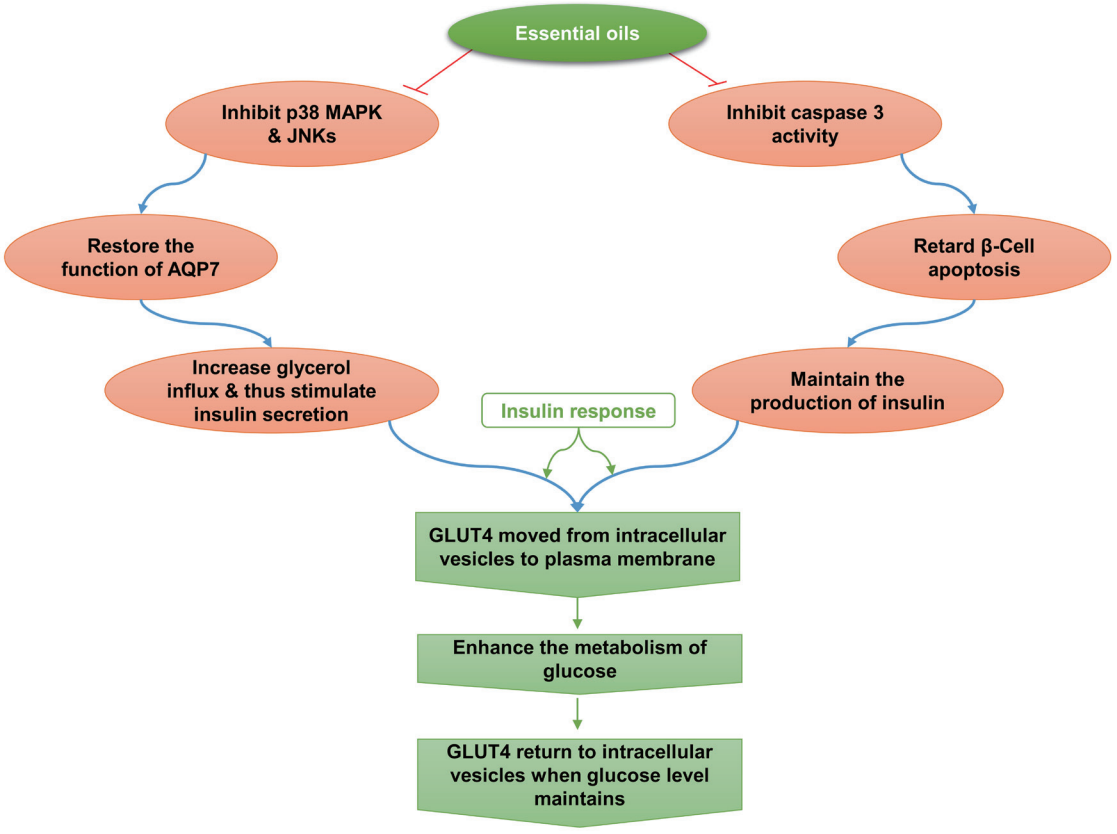

Fig. 7. Anti-diabetic mechanism of essential oils through signaling pathways. AQP, aquaporin; GLUT4, glucose transporter protein type-4; JNKs, jun amino-terminal kinases; MAPK, mitogen-activated protein kinase.

abolic enzymes in streptozotocin-induced diabetic rats. Additionally, it successfully inhibited α-amylase.[137] *Lavandula stoechas* L. (Lavender) essential oils exhibited an antihyperglycemic effect in alloxan-induced diabetic rats by protecting against oxidative stress and decreasing lipid peroxidation through the activation of endogenous antioxidant enzymes.[138]

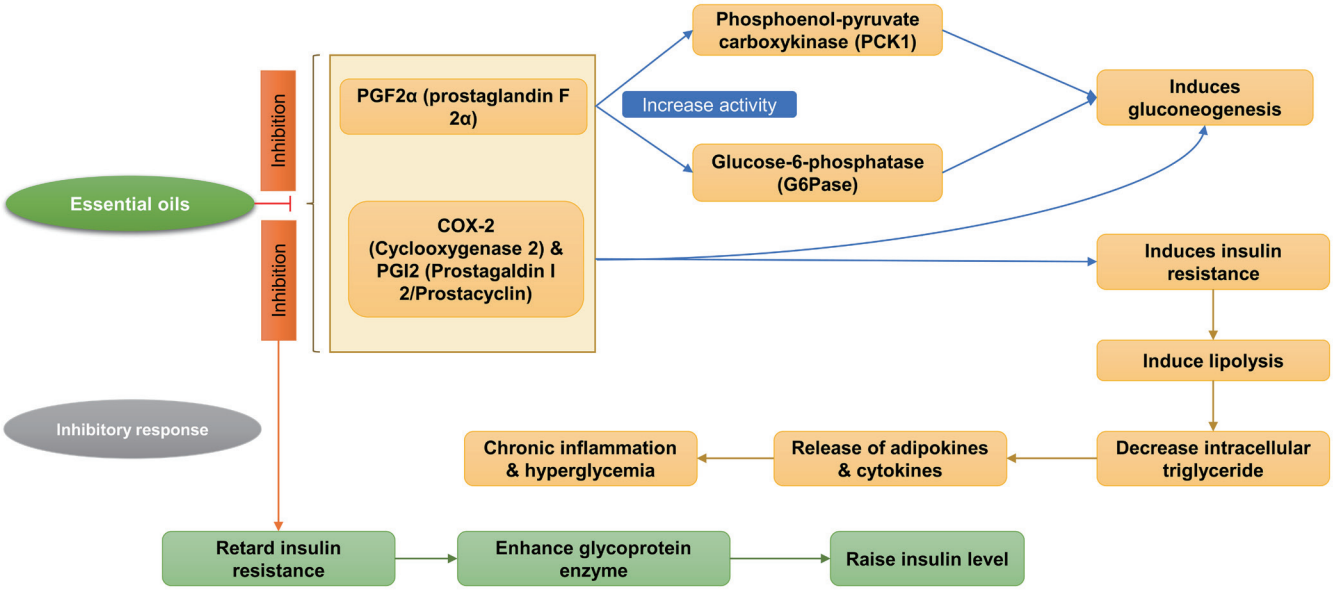

Fig. 8. Anti-diabetic mechanism of essential oils via inhibition of prostaglandins.

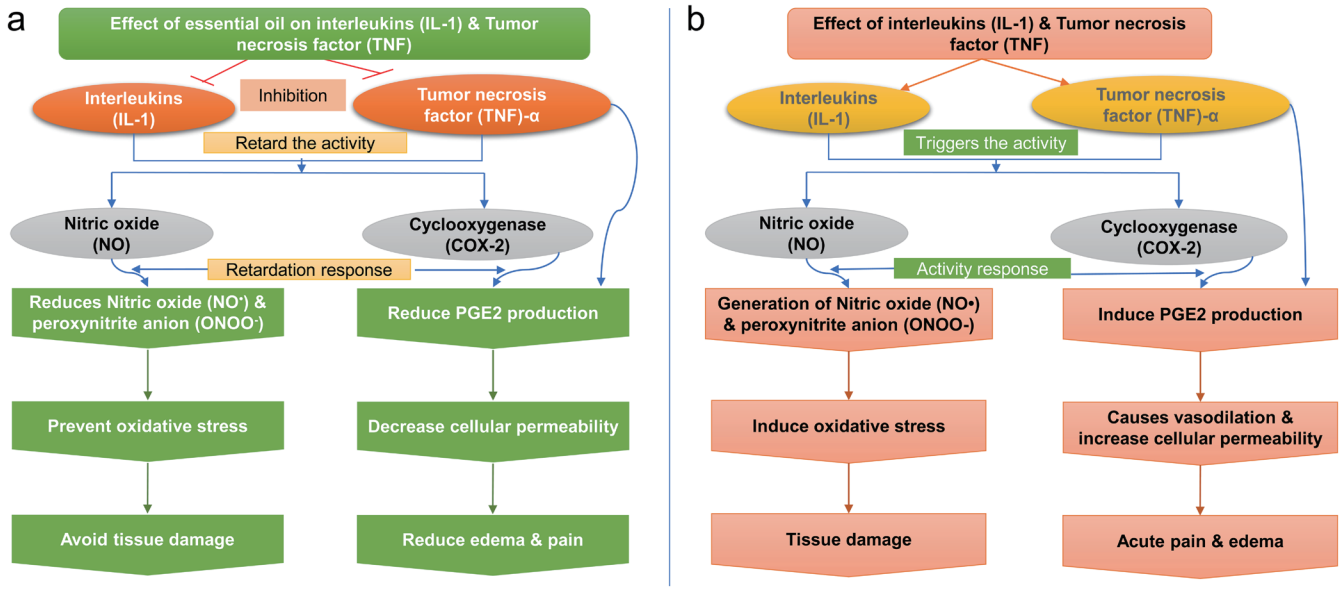

Fig. 9. Inflammatory response of interleukins and TNF and curative mechanism of essential oils. (a) Effect of essential oil on interleukins and TNF. (b) Function of interleukins and TNF. PGE2, prostaglandin E2.

Origanum compactum essential oil showed potential anti-diabetic activity through inhibition of α-amylase and α-glucosidase. Carvacrol and thymol, components of essential oil, showed the best binding affinity towards the enzymes and modulated their activities.[139] Black pepper essential oil showed stronger inhibition against *α*-glucosidase than *α*-amylase. It alters the blood glucose level by reducing starch catabolism.[140]

Anti-inflammatory role of essential oils

Inflammation is a fundamental protective response triggered by tissue damage or infection, serving as a defense mechanism against pathogens and facilitating the removal of damaged host cells. The inflammatory response leads to increased permeability of the endothelial lining, influx of blood leukocytes into the interstitial space, an oxidative burst, and the release of cytokines. It also promotes the metabolism of arachidonic acid, enhancing the activity of various enzymes and free radicals. Essential oils can counteract edema formation by reducing elevated levels of arachidonic acid derivatives, such as prostaglandins and leukotrienes, thus demonstrating their potential to modulate inflammatory responses.[141–143]

Anti-inflammatory mechanism of essential oils

Cytokine is a group of pro-inflammatory interleukins (IL-1-*β*, TNF-*α*, IL-6, IL-15, IL-17, and IL-18), anti-inflammatory interleukins (IL-4, IL-10, and IL-13), interferon-γ, TNF-α. TNF-α is responsible for vasodilation and increase of vascular permeability, which leads to systemic edema.[144] Leukotriene B4 encourages macrophage degranulation and activated neutrophils to produce superoxide.[145] The excess amount of superoxide damages tissues via oxidative stress by reducing the activation and proliferation of T lymphocytes. IL-1 and TNF trigger the activity of phospholipase (PL) A2, COX-2, and nitric oxide (NO) synthase that increases the production of platelet-activating factor, leukotrienes, prostanoids and nitric oxide. IL-1 and TNF are also responsible for endothelial adhesion and emigration of leukotriene into the tissues, where they activate neutrophils and produce inflammation, loss of functioning, and tissue damage. IL-8 also activate neutrophils, leading to degradation of tissues.[146] The anti-inflammatory interleukins (IL-4, IL-10, and IL-13) and transforming growth factor-β conquer the synthesis of IL-1, TNF, and IL-8. Inhibition of COX-2 enzyme leads to the inhibition of the production of inflammatory mediators like prostaglandins (PGE2) and thromboxanes. PGE2 is responsible for vasodilation, acute pain, and edema. The excess production of nitric oxide generates nitric oxide ($NO^{\bullet}$) and peroxynitrite anion ($ONOO^{-}$) radicals (Fig. 9).

Oxidative burst, an inflammatory trigger, results from a dramatic increase in oxygen consumption, leading to the formation of superoxide anion radical ($O_2^{\bullet-}$). This radical can naturally transition to hydrogen peroxide or be converted by superoxide dismutase. Transition metals can further process hydrogen peroxide into hydroxyl radical, which reacts with polyunsaturated fatty acids to produce peroxyl radicals. Hydrogen peroxide can also form hypochlorous acid by oxidizing halide ions. These radicals and reactive species cause oxidative damage to tissues by affecting proteins, phosphatases, lipid kinases, membrane receptors, ion channels, and transcription factors like nuclear factor-κB (NF-κB), ultimately leading to the modulation of inflammatory responses (Fig. 10).[147]

Essential oils work as an anti-inflammatory agent by inhibiting the effect of pro-inflammatory cytokines, prostaglandins, and phospholipase, scavenging free radicals, protecting from oxidative bursts, and decreasing vascular permeability.

Works that reflect the anti-inflammatory activity of essential oils

Essential oil of both the male and female species of *Baccharis punctulata* decreases the activity of myeloperoxidase enzyme, which is produced after insertion of 12-O-tetradecanoylphorbol-13-acetate for the induction of inflammation. It also inhibits inflammatory cell migration.[148] It activates hypochlorous acid production, a highly cytotoxic compound with high diffusivity and

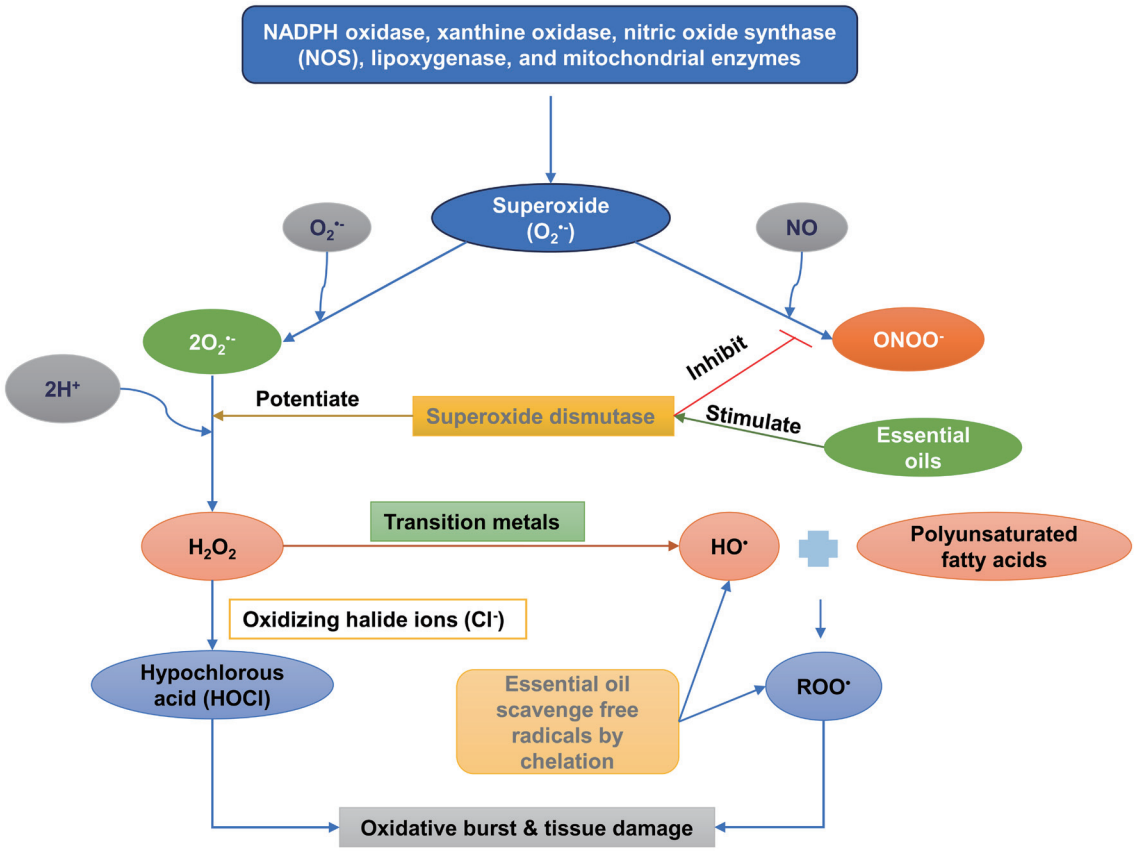

Fig. 10. Protection against oxidative burst by essential oil. HO•, hydroxyl radical; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NO, nitric oxide; $ONOO^-$, peroxynitrite anion; $ROO^•$, peroxyl radicals.

oxidative activity,[149] reacts with lipids, proteins, and nucleic acids, and produces a degradative effect on various tissues and developed diseases like lung inflammation, inflammatory bowel disease, rheumatoid arthritis, cystic fibrosis, sinusitis etc.[150]

The *Pogostemon benghalensis* (Burm.F.) Kuntze essential oil showed significant anti-inflammatory activity when assayed for carrageenan-induced paw edema, xylene-induced ear edema, cotton pellet-induced granuloma, acetic acid-induced abdominal writhing, and ethanol-induced gastric ulcer. It was concluded that it worked by inhibiting the release of inflammation causative agents, macrophage induction, and release of phospholipase, histamine, kinin, and fibrinolysin mediators. It diminishes cytokinin-mediated responses, provides gastric cytoprotection, and reduces vascular permeability.[151]

Zanthoxylum myriacanthum var. *pubescens* Huang essential oil inhibited nitric oxide production in dose-dependent manner in LPS-induced RAW 264.7 cells.[152] *Campomanesia phaea* essential oil gives a marked decrease in the production of IL-6, TNF-α, NO, superoxide radical, and NF-κB activity when assayed for anti-inflammatory activity.[153]

Moringa oleifera Lam essential oil protects proteins from denaturation and maintains the stability of the membrane.[154] Protein denaturation is a biochemical process that disrupts the hydrogen, hydrophobic, and disulfide bonds, which leads to alteration in the structure of the protein.[155] It is indicated by certain inflammatory responses like redness, pain, heat, swelling, and loss of function of tissues in that area, which makes it susceptible to enzymatic hydrolysis.[156] Lysosomal enzymes produce autoantigens, alter the mucosal barrier, and increase cytokine secretions.[157]

Chamaecyparis obtuse essential oil inhibited the expression of cyclooxygenase, reduced the production of PGE2, and diminished the expression of TNF-α when assayed for anti-inflammatory effect.[158] *Eucalyptus globulus* essential oil showed anti-inflammatory activity when assayed. It inhibits protein denaturation and diminishes prostaglandins and cytokines production at the dose of 250 µg/mL.[159] The essential oil of *Lavandula angustifolia* Mill flowers of the beginning stage significantly reduces interleukins IL-1, IL-8, and NF-κB.[160]

Conclusions

The molecular mechanisms underlying the therapeutic potential of essential oils remain a complex challenge yet to be fully understood. Numerous studies are underway to explore these potentials further. The current review represents an effort to collate and examine various pathways and mechanisms through which essential oils exert their antioxidant, antimicrobial, anticarcinogenic, antidiabetic, and anti-inflammatory effects. While several researchers have endeavored to pinpoint the exact mechanisms of action based on experimental findings, a comprehensive understanding of the stepwise pathways and the full scope of essential oils' potential necessitates further in-depth research. This work is a step towards unraveling and elucidating the myriad mechanisms by which essential oils may benefit health and treat diseases.

Acknowledgments

None.

Funding

None.

Conflict of interest

The author has no conflict of interest related to this publication.

Author contributions

RK is the sole author of the manuscript.

References

[1] Kar S, Gupta P, Gupta J. Essential oils: biological activity beyond aromatherapy. Nat Prod Sci 2018;24(3):139–147. doi:10.20307/nps.2018.24.3.139.
[2] Figueiredo AC. Biological properties of essential oils and volatiles: Sources of variability. Nat Volatiles & Essent Oils 2017;4(4):1–13.
[3] Zhang Y, Tang J, Liu Q, Ge J, Ma Z, Mou J, *et al*. Biological, functional and network pharmacological exploration of essential oils in treatment and healthcare of human diseases. Future Integr Med 2023;2(1):23–31. doi:10.14218/FIM.2022.00038.
[4] Zukowska G, Durczynska Z. Properties and applications of essential oils: a review. JEE 2024;25(2):333–340. doi:10.12911/22998993/177404.
[5] Tavassoly I, Goldfarb J, Iyengar R. Systems biology primer: the basic methods and approaches. Essays Biochem 2018;62(4):487–500. doi:10.1042/EBC20180003, PMID:30287586.
[6] Tkacik G, Bialek W. Cell biology: networks, regulation and pathways. In: Meyers RC (ed). Encyclopedia of complexity and systems science. New York: Springer; 2009:719–741. doi:10.1007/978-0-387-30440-3_48.
[7] Mast FD, Ratushny AV, Aitchison JD. Systems cell biology. J Cell Biol 2014;206(6):695–706. doi:10.1083/jcb.201405027, PMID:25225336.
[8] Pandey AK, Kumar P, Singh P, Tripathi NN, Bajpai VK. Essential Oils: Sources of Antimicrobials and Food Preservatives. Front Microbiol 2016;7:2161. doi:10.3389/fmicb.2016.02161, PMID:28138324.
[9] Hyldgaard M, Mygind T, Meyer RL. Essential oils in food preservation: mode of action, synergies, and interactions with food matrix components. Front Microbiol 2012;3:12. doi:10.3389/fmicb.2012.00012, PMID:22291693.
[10] Su LJ, Zhang JH, Gomez H, Murugan R, Hong X, Xu D, *et al*. Reactive Oxygen Species-Induced Lipid Peroxidation in Apoptosis, Autophagy, and Ferroptosis. Oxid Med Cell Longev 2019;2019:5080843. doi:10.1155/2019/5080843, PMID:31737171.
[11] Harayama T, Riezman H. Understanding the diversity of membrane lipid composition. Nat Rev Mol Cell Biol 2018;19(5):281–296. doi:10.1038/nrm.2017.138, PMID:29410529.
[12] Li Y, Si D, Sabier M, Liu J, Si J, Zhang X. Guideline for screening antioxidant against lipid-peroxidation by spectrophotometer. eFood 2023;4(4):e80. doi:10.1002/efd2.80.
[13] Ramana KV, Srivastava S, Singhal SS. Lipid peroxidation products in human health and disease 2014. Oxid Med Cell Longev 2014;2014:162414. doi:10.1155/2014/162414, PMID:25302089.
[14] Manjamalai A, Berlin Grace VM. Antioxidant activity of essential oils from Wedelia chinensis (Osbeck) in vitro and in vivo lung cancer bearing C57BL/6 mice. Asian Pac J Cancer Prev 2012;13(7):3065–3071. doi:10.7314/apjcp.2012.13.7.3065, PMID:22994711.
[15] Dontha S. A review on antioxidant methods. Asian J Pharm Clin Res 2016;9(8):14–32. doi:10.22159/ajpcr.2016.v9s2.13092.
[16] Devasagayam TP, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD. Free radicals and antioxidants in human health: current status and future prospects. J Assoc Physicians India 2004;52:794–804. PMID:15909857.
[17] Mohamed AA, Alotaibi BM. Essential oils of some medicinal plants and their biological activities: A mini review. J Umm Al-Qura Univ Appl Sci 2023;9:40–49. doi:10.1007/s43994-022-00018-1.
[18] Kebede BH, Forsido SF, Tola YB, Astatkie T. Free radical scavenging capacity, antibacterial activity and essential oil composition of turmeric (Curcuma domestica) varieties grown in Ethiopia. Heliyon 2021;7(2):e06239. doi:10.1016/j.heliyon.2021.e06239, PMID:33659752.
[19] Foti MC, Ingold KU. Mechanism of inhibition of lipid peroxidation by gamma-terpinene, an unusual and potentially useful hydrocarbon antioxidant. J Agric Food Chem 2003;51(9):2758–2765. doi:10.1021/jf020993f, PMID:12696969.
[20] de Sousa DP, Damasceno ROS, Amorati R, Elshabrawy HA, de Castro RD, Bezerra DP, *et al*. Essential Oils: Chemistry and Pharmacological Activities. Biomolecules 2023;13(7):1144. doi:10.3390/biom13071144, PMID:37509180.
[21] Sultan MT, Butt MS, Karim R, Ahmed W, Kaka U, Ahmad S, *et al*. Nigella sativa fixed and essential oil modulates glutathione redox enzymes in potassium bromate induced oxidative stress. BMC Complement Altern Med 2015;15:330. doi:10.1186/s12906-015-0853-7, PMID:26385559.
[22] El Hachlafi N, Fikri-Benbrahim K, Al-Mijalli SH, Elbouzidi A, Jeddi M, Abdallah EM, *et al*. Tetraclinis articulata (Vahl) Mast. essential oil as a promising source of bioactive compounds with antimicrobial, antioxidant, anti-inflammatory and dermatoprotective properties: In vitro and in silico evidence. Heliyon 2024;10(1):e23084. doi:10.1016/j.heliyon.2023.e23084, PMID:38169772.
[23] Riberio B. Glutathione: the master antioxidant. Ozone Ther Glob J 2023;13(1):175–197.
[24] Ridaoui K, Guenaou I, Taouam I, Cherki M, Bourhim N, Elamrani A, *et al*. Comparative study of the antioxidant activity of the essential oils of five plants against the H(2)O(2) induced stress in Saccharomyces cerevisiae. Saudi J Biol Sci 2022;29(3):1842–1852. doi:10.1016/j.sjbs.2021.10.040, PMID:35280527.
[25] Rosa AC, Corsi D, Cavi N, Bruni N, Dosio F. Superoxide Dismutase Administration: A Review of Proposed Human Uses. Molecules 2021;26(7):1844. doi:10.3390/molecules26071844, PMID:33805942.
[26] Trist BG, Hilton JB, Hare DJ, Crouch PJ, Double KL. Superoxide Dismutase 1 in Health and Disease: How a Frontline Antioxidant Becomes Neurotoxic. Angew Chem Int Ed Engl 2021;60(17):9215–9246. doi:10.1002/anie.202000451, PMID:32144830.
[27] Fujii J, Homma T, Osaki T. Superoxide Radicals in the Execution of Cell Death. Antioxidants (Basel) 2022;11(3):501. doi:10.3390/antiox11030501, PMID:35326151.
[28] Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria J Med 2018;54(4):287–293. doi:10.1016/j.ajme.2017.09.001.
[29] Fukai T, Ushio-Fukai M. Superoxide dismutases: role in redox signaling, vascular function, and diseases. Antioxid Redox Signal 2011;15(6):1583–1606. doi:10.1089/ars.2011.3999, PMID:21473702.
[30] Gayashani Sandamalika WM, Kwon H, Lim C, Yang H, Lee J. The possible role of catalase in innate immunity and diminution of cellular oxidative stress: Insights into its molecular characteristics, antioxidant activity, DNA protection, and transcriptional regulation in response to immune stimuli in yellowtail clownfish (Amphiprion clarkii). Fish Shellfish Immunol 2021;113:106–117. doi:10.1016/j.fsi.2021.03.022, PMID:33826938.
[31] Nandi A, Yan LJ, Jana CK, Das N. Role of Catalase in Oxidative Stress- and Age-Associated Degenerative Diseases. Oxid Med Cell Longev 2019;2019:9613090. doi:10.1155/2019/9613090, PMID:31827713.
[32] Goyal MM, Basak A. Human catalase: looking for complete identity. Protein Cell 2010;1(10):888–897. doi:10.1007/s13238-010-0113-z, PMID:21204015.
[33] Alfonso-Prieto M, Biarnés X, Vidossich P, Rovira C. The molecular mechanism of the catalase reaction. J Am Chem Soc 2009;131(33):11751–11761. doi:10.1021/ja9018572, PMID:19653683.
[34] Król M, Kepinska M. Human Nitric Oxide Synthase-Its Functions, Polymorphisms, and Inhibitors in the Context of Inflammation, Diabetes and Cardiovascular Diseases. Int J Mol Sci 2020;22(1):56. doi:10.3390/ijms22010056, PMID:33374571.

[35] Carlstrom M, Montenegro MF. Therapeutic value of stimulating the nitrate-nitrite-nitric oxide pathway to attenuate oxidative stress and restore nitric oxide bioavailability in cardiorenal disease. J Intern Med 2019;285(1):2–18. doi:10.1111/joim.12818, PMID:30039620.
[36] Lundberg JO, Weitzberg E. Nitric oxide signaling in health and disease. Cell 2022;185(16):2853–2878. doi:10.1016/j.cell.2022.06.010, PMID:35931019.
[37] Papi S, Ahmadizar F, Hasanvand A. The role of nitric oxide in inflammation and oxidative stress. Immunopathol Persa 2019;5(1):e08. doi:10.15171/ipp.2019.08.
[38] Lubos E, Handy DE, Loscalzo J. Role of oxidative stress and nitric oxide in atherothrombosis. Front Biosci 2008;13:5323–5344. doi:10.2741/3084, PMID:18508590.
[39] Sohilait HJ, Kainama H. Free Radical Scavenging Activity of Essential Oil of Eugenia caryophylata from Amboina Island and Derivatives of Eugenol. Open Chem 2019;17(1):422–428. doi:10.1515/chem-2019-0047.
[40] da Costa LS, de Moraes ÂAB, Cruz JN, Mali SN, Almeida LQ, do Nascimento LD, *et al*. First Report on the Chemical Composition, Antioxidant Capacity, and Preliminary Toxicity to Artemia salina L. of Croton campinarensis Secco, A. Rosário & PE Berry (Euphorbiaceae) Essential Oil, and In Silico Study. Antioxidants (Basel) 2022;11(12):2410. doi:10.3390/antiox11122410, PMID:36552618.
[41] Dadashpour M, Rasooli I, Sefidkon F, Rezaei MB, Astaneh DAS. Lipid peroxidation inhibition, superoxide anion and nitric oxide radical scavenging properties of Thymus daenensis and Anethum graveolens essential oils. J Med Plant Res 2011;10(37):109–120.
[42] Tit DM, Bungau SG. Antioxidant Activity of Essential Oils. Antioxidants (Basel) 2023;12(2):383. doi:10.3390/antiox12020383, PMID: 36829942.
[43] Goze I, Alim A, Tepe AS, Sokmen M, Sevgi K, Tepe B. Screening of the antioxidant activity of essential oil and various extracts of Origanum rotundifolium Boiss. from Turkey. J Med Plant Res 2009;3(4):246–254.
[44] Amiri H. Essential oils composition and antioxidant properties of three thymus species. Evid Based Complement Alternat Med 2012;2012:728065. doi:10.1155/2012/728065, PMID:21876714.
[45] Cioanca O, Mircea C, Hritcu L, Trifan A, Mihasan M, Aprotosoaie AC, *et al*. In vitro - in vivo correlation of the antioxidant capacity of Salviae aetheroleum essential oil. Farmacia 2015;63(1):34–39.
[46] Burits M, Bucar F. Antioxidant activity of Nigella sativa essential oil. Phytother Res 2000;14(5):323–328. doi:10.1002/1099-1573(200008)14:5<323::aid-ptr621>3.0.co;2-q, PMID:10925395.
[47] Farias PKL, Silva JCRL, Souza CND, Fonseca FSAD, Brandi IV, Martins ER, *et al*. Antioxidant activity of essential oils from condiment plants and their effect on lactic cultures and pathogenic bacteria. Cienc Rural 2019;49(2):1–12. doi:10.1590/0103-8478cr20180140.
[48] Kumar V, Mathela CS, Kumar M, Tewari G. Antioxidant potential of essential oils from some Himalayan Asteraceae and Lamiaceae species. Med Drug Discov 2019;1:100004. doi:10.1016/j.medidd.2019.100004.
[49] Rahman A, Afroj M, Islam R, Islam KD, Hossain MA, Na M. In vitro antioxidant potential of the essential oil and leaf extracts of Curcuma zedoaria Rosc. J Appl Pharm Sci 2014;4(2):107–111. doi:10.7324/JAPS.2014.40217.
[50] Inaam El, Sara H, Saadia L, Mohamed E, Abdesalam L. Study of antioxidant activity of essential oils extracted from Moroccan medicinal and aromatic plants. European J Med Plants 2015;10(2):1–12. doi:10.9734/EJMP/2015/19955.
[51] Oluyele O, Oladunmoye MK, Ogundare AO. Antioxidant potential of essential oil from Phoenix dactylifera (L.) seed. GSC Biol Pharm Sci 2022;19(2):014–022. doi:10.30574/gscbps.2022.19.2.0139.
[52] Ozkan A, Erdogan A, Sokmem M, Tugrulay S, Unal O. Antitumoral and antioxidant effect of essential oils and in vitro antioxidant properties of essential oils and aqueous extracts from Salvia pisidica. Biologia 2010;65(6):990–996. doi:10.2478/s11756-010-0108-5.
[53] Yap PSX, Yusoff K, Lim SHE, Chong CM, Lai KS. Membrane disruption properties of essential oils-A double-edged sword? Processes 2021;9(4):595. doi:10.3390/pr9040595.
[54] Wu K, Lin Y, Chai X, Duan X, Zhao X, Chun C. Mechanisms of vapor-phase antibacterial action of essential oil from Cinnamomum camphora var. linaloofera Fujita against Escherichia coli. Food Sci Nutr 2019;7(8):2546–2555. doi:10.1002/fsn3.1104, PMID:31428342.
[55] Zhang J, Ye KP, Zhang X, Pan DD, Sun YY, Cao JX. Antibacterial Activity and Mechanism of Action of Black Pepper Essential Oil on Meat-Borne Escherichia coli. Front Microbiol 2016;7:2094. doi:10.3389/fmicb.2016.02094, PMID:28101081.
[56] Yuan C, Hao X. Antibacterial mechanism of action and in silico molecular docking studies of Cupressus funebris essential oil against drug resistant bacterial strains. Heliyon 2023;9(8):e18742. doi:10.1016/j.heliyon.2023.e18742, PMID:37636470.
[57] Dias C, Nylandsted J. Plasma membrane integrity in health and disease: significance and therapeutic potential. Cell Discov 2021;7(1):4. doi:10.1038/s41421-020-00233-2, PMID:33462191.
[58] McCarthy JV, Cotter TG. Cell shrinkage and apoptosis: a role for potassium and sodium ion efflux. Cell Death Differ 1997;4(8):756–770. doi:10.1038/sj.cdd.4400296, PMID:16465288.
[59] Bortner CD, Hughes FM Jr, Cidlowski JA. A primary role for K+ and Na+ efflux in the activation of apoptosis. J Biol Chem 1997;272(51):32436–42. doi:10.1074/jbc.272.51.32436, PMID:9405453.
[60] Owen L, White AW, Laird K. Characterisation and screening of antimicrobial essential oil components against clinically important antibiotic-resistant bacteria using thin layer chromatography-direct bioautography hyphenated with GC-MS, LC-MS and NMR. Phytochem Anal 2019;30(2):121–131. doi:10.1002/pca.2797, PMID:30280447.
[61] Bouyahya A, Abrini J, Dakka N, Bakri Y. Essential oils of Origanum compactum increase membrane permeability, disturb cell membrane integrity, and suppress quorum-sensing phenotype in bacteria. J Pharm Anal 2019;9(5):301–311. doi:10.1016/j.jpha.2019.03.001, PMID:31929939.
[62] Mangalagiri NP, Velagapudi K, Panditi SK, Jeevigunta NLL. Mechanism of action of essential oils and their major components. Research & Reviews: J Bot 2021;10(3):33–43. doi:10.37591/RRJoB.
[63] Yang XN, Khan I, Kang SC. Chemical composition, mechanism of antibacterial action and antioxidant activity of leaf essential oil of Forsythia koreana deciduous shrub. Asian Pac J Trop Med 2015;8(9):694–700. doi:10.1016/j.apjtm.2015.07.031, PMID:26433652.
[64] Issa D, Najjar A, Greige-Gerges H, Nehme H. Screening of Some Essential Oil Constituents as Potential Inhibitors of the ATP Synthase of Escherichia coli. J Food Sci 2019;84(1):138–146. doi:10.1111/1750-3841.14421, PMID:30569590.
[65] Chen Y, Zhao J, Liu C, Wu D, Wang X. In-vitro antibacterial activity and mechanism of Monarda didyma essential oils against Carbapenem-resistant Klebsiella pneumoniae. BMC Microbiol 2023;23(1):263. doi:10.1186/s12866-023-03015-4, PMID:37730531.
[66] Babaei G, Gholizadeh-Ghaleh Aziz S, Rajabi Bazl M, Khadem Ansari MH. A comprehensive review of anticancer mechanisms of action of Alantolactone. Biomed Pharmacother 2021;136:111231. doi:10.1016/j.biopha.2021.111231, PMID:33454597.
[67] Amjad E, Sokouti B, Asnaashari S. A systematic review of anti-cancer roles and mechanisms of kaempferol as a natural compound. Cancer Cell Int 2022;22(1):260. doi:10.1186/s12935-022-02673-0, PMID:35986346.
[68] Mohamed Abdoul-Latif F, Ainane A, Houmed Aboubaker I, Mohamed J, Ainane T. Exploring the Potent Anticancer Activity of Essential Oils and Their Bioactive Compounds: Mechanisms and Prospects for Future Cancer Therapy. Pharmaceuticals (Basel) 2023;16(8):1086. doi:10.3390/ph16081086, PMID:37631000.
[69] Zishan M, Saidurrahman S, Azeemuddin A, Ahmad Z, Hussain MW. Natural products used as anti-cancer agents. J Drug Deliv Ther 2017;7(3):11–18. doi:10.22270/jddt.v7i3.1443.
[70] Ramel C, Alekperov UK, Ames BN, Kada T, Wattenberg LW. International Commission for Protection Against Environmental Mutagens and Carcinogens. ICPEMC Publication No. 12. Inhibitors of mutagenesis and their relevance to carcinogenesis. Report by ICPEMC Expert Group on Antimutagens and Desmutagens. Mutat Res 1986;168(1):47–65. doi:10.1016/0165-1110(86)90021-7, PMID:3520303.
[71] De Flora S, Ramel C. Mechanisms of inhibitors of mutagenesis and carcinogenesis. Classification and overview. Mutat Res 1988;202(2):285–306. doi:10.1016/0027-5107(88)90193-5, PMID:3057362.
[72] Gudi VA, Singh SV. Effect of diallyl sulfide, a naturally occurring anti-

carcinogen, on glutathione-dependent detoxification enzymes of female CD-1 mouse tissues. Biochem Pharmacol 1991;42(6):1261–1265. doi:10.1016/0006-2952(91)90263-5, PMID:1888335.
[73] Kim ND, Kim SG, Kwak MK. Enhanced expression of rat microsomal epoxide hydrolase gene by organosulfur compounds. Biochem Pharmacol 1994;47(3):541–547. doi:10.1016/0006-2952(94)90186-4, PMID:8117322.
[74] Nakamura Y, Miyamoto M, Murakami A, Ohigashi H, Osawa T, Uchida K. A phase II detoxification enzyme inducer from lemongrass: identification of citral and involvement of electrophilic reaction in the enzyme induction. Biochem Biophys Res Commun 2003;302(3):593–600. doi:10.1016/s0006-291x(03)00219-5, PMID:12615076.
[75] Jancova P, Anzenbacher P, Anzenbacherova E. Phase II drug metabolizing enzymes. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2010;154(2):103–116. doi:10.5507/bp.2010.017, PMID: 20668491.
[76] Kapur A, Felder M, Fass L, Kaur J, Czarnecki A, Rathi K, *et al*. Modulation of oxidative stress and subsequent induction of apoptosis and endoplasmic reticulum stress allows citral to decrease cancer cell proliferation. Sci Rep 2016;6:27530. doi:10.1038/srep27530, PMID:27270209.
[77] Sanches LJ, Marinello PC, Panis C, Fagundes TR, Morgado-Díaz JA, de-Freitas-Junior JC, *et al*. Cytotoxicity of citral against melanoma cells: The involvement of oxidative stress generation and cell growth protein reduction. Tumour Biol 2017;39(3):1010428317695914. doi:10.1177/1010428317695914, PMID:28351318.
[78] Dudai N, Weinstein Y, Krup M, Rabinski T, Ofir R. Citral is a new inducer of caspase-3 in tumor cell lines. Planta Med 2005;71(5):484–488. doi:10.1055/s-2005-864146, PMID:15931590.
[79] Arunasree KM. Anti-proliferative effects of carvacrol on a human metastatic breast cancer cell line, MDA-MB 231. Phytomedicine 2010;17(8-9):581–588. doi:10.1016/j.phymed.2009.12.008, PMID:20096548.
[80] Girola N, Figueiredo CR, Farias CF, Azevedo RA, Ferreira AK, Teixeira SF, *et al*. Camphene isolated from essential oil of Piper cernuum (Piperaceae) induces intrinsic apoptosis in melanoma cells and displays antitumor activity in vivo. Biochem Biophys Res Commun 2015;467(4):928–934. doi:10.1016/j.bbrc.2015.10.041, PMID:26471302.
[81] Liu B, Xue Q, Tang Y, Cao J, Guengerich FP, Zhang H. Mechanisms of mutagenesis: DNA replication in the presence of DNA damage. Mutat Res Rev Mutat Res 2016;768:53–67. doi:10.1016/j.mrrev.2016.03.006, PMID:27234563.
[82] Elfaki I, Mir R, Almutairi FM, Duhier FMA. Cytochrome P450: Polymorphisms and Roles in Cancer, Diabetes and Atherosclerosis. Asian Pac J Cancer Prev 2018;19(8):2057–2070. doi:10.22034/APJCP.2018.19.8.2057, PMID:30139042.
[83] Reed L, Arlt VM, Phillips DH. The role of cytochrome P450 enzymes in carcinogen activation and detoxication: an in vivo-in vitro paradox. Carcinogenesis 2018;39(7):851–859. doi:10.1093/carcin/bgy058, PMID:29726902.
[84] Sanchez-Dominguez CN, Gallardo-Blanco HL, Salinas-Santander MA, Ortiz-Lopez R. Uridine 5'-diphospho-glucronosyltrasferase: Its role in pharmacogenomics and human disease. Exp Ther Med 2018;16(1):3–11. doi:10.3892/etm.2018.6184, PMID:29896223.
[85] Singh RR, Reindl KM. Glutathione S-Transferases in Cancer. Antioxidants (Basel) 2021;10(5):701. doi:10.3390/antiox10050701, PMID: 33946704.
[86] Potęga A. Glutathione-Mediated Conjugation of Anticancer Drugs: An Overview of Reaction Mechanisms and Biological Significance for Drug Detoxification and Bioactivation. Molecules 2022;27(16):5252. doi:10.3390/molecules27165252, PMID:36014491.
[87] Guengerich FP, Peterson LA, Cmarik JL, Koga N, Inskeep PB. Activation of dihaloalkanes by glutathione conjugation and formation of DNA adducts. Environ Health Perspect 1987;76:15–8. doi:10.1289/ehp.877615, PMID:3329096.
[88] Wilce MCJ, Parker MW. Structure and function of glutathione S-transferases. Biochimica et Biophysica Acta 1994;1205(1):1–18. doi:10.1016/0167-4838(94)90086-8.
[89] de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans. Pharmacogenetic and developmental aspects. Clin Pharmacokinet 1999;36(6):439–452. doi:10.2165/00003088-199936060-00005, PMID:10427468.
[90] Izumi K, Inoue S, Ide H, Fujita K, Mizushima T, Jiang G, *et al*. Uridine 5'diphospho-glucuronosyltransferase 1A expression as an independent prognosticator in urothelial carcinoma of the upper urinary tract. Int J Urol 2018;25(5):429–435. doi:10.1111/iju.13528, PMID:29444544.
[91] Fischer AH, Wong JYY, Baris D, Koutros S, Karagas MR, Schwenn M, *et al*. Urine pH and Risk of Bladder Cancer in Northern New England. Cancer Epidemiol Biomarkers Prev 2023;32(10):1323–1327. doi:10.1158/1055-9965.EPI-22-0801, PMID:37351876.
[92] Freudenthal RI, Stephens E, Anderson DP. Determining the Potential of Aromatic Amines to Induce Cancer of the Urinary Bladder. International Journal of Toxicology 1999;18(5):353–359. doi:10.1080/109158199225260.
[93] Cavelier G, Amzel LM. Mechanism of NAD(P)H:quinone reductase: Ab initio studies of reduced flavin. Proteins 2001;43(4):420–432. doi:10.1002/prot.1055, PMID:11340659.
[94] Oesch F, Hengstler JG, Arand M. Detoxication strategy of epoxide hydrolase-the basis for a novel threshold for definable genotoxic carcinogens. Nonlinearity Biol Toxicol Med 2004;2(1):21–26. doi:10.1080/15401420490426963, PMID:19330105.
[95] Toscano-Garibay JD, Arriaga-Alba M, Sánchez-Navarrete J, Mendoza-García M, Flores-Estrada JJ, Moreno-Eutimio MA, *et al*. Antimutagenic and antioxidant activity of the essential oils of Citrus sinensis and Citrus latifolia. Sci Rep 2017;7(1):11479. doi:10.1038/s41598-017-11818-5, PMID:28904369.
[96] Vuković-Gacić B, Nikcević S, Berić-Bjedov T, Knezević-Vukcević J, Simić D. Antimutagenic effect of essential oil of sage (Salvia officinalis L.) and its monoterpenes against UV-induced mutations in Escherichia coli and Saccharomyces cerevisiae. Food Chem Toxicol 2006;44(10):1730–1738. doi:10.1016/j.fct.2006.05.011, PMID:16814443.
[97] Yang Y, Yue Y, Runwei Y, Guolin Z. Cytotoxic, apoptotic and antioxidant activity of the essential oil of Amomum tsao-ko. Bioresour Technol 2010;101(11):4205–4211. doi:10.1016/j.biortech.2009.12.131, PMID:20133123.
[98] Suhail MM, Wu W, Cao A, Mondalek FG, Fung KM, Shih PT, *et al*. Boswellia sacra essential oil induces tumor cell-specific apoptosis and suppresses tumor aggressiveness in cultured human breast cancer cells. BMC Complement Altern Med 2011;11:129. doi:10.1186/1472-6882-11-129, PMID:22171782.
[99] Silva SLD, Chaar JDS, Figueiredo PDMS, Yano T. Cytotoxic evaluation of essential oil from Casearia sylvestris on human cancer cells and erythrocytes. Acta Amazon 2008;38(1):107–112. doi:10.1590/S0044-59672008000100012.
[100] Amiel E, Ofir R, Dudai N, Soloway E, Rabinsky T, Rachmilevitch S. β-Caryophyllene, a Compound Isolated from the Biblical Balm of Gilead (Commiphora gileadensis), Is a Selective Apoptosis Inducer for Tumor Cell Lines. Evid Based Complement Alternat Med 2012;2012:872394. doi:10.1155/2012/872394, PMID:22567036.
[101] Cetinus E, Temiz T, Ergul M, Altun A, Cetinus S, Kaya T. Thyme essential oil inhibits proliferation of DLD-1 colorectal cancer cells through antioxidant effect. Cumhur Medical J 2013;35(1):14–24. doi:10.7197/1305-0028.1757.
[102] Javed A, Subasini U, Muath SMA, Esra TA. Essential oil composition and antidiabetic, anticancer activity of Rosmarinus officinalis L. Leaves from Erbil (Iraq). J Essent Oil-Bear Plants 2020;22(6):1544–1553. doi:10.1080/0972060X.2019.1689179.
[103] Patil JR, Jayaprakasha GK, Chidambara Murthy KN, Tichy SE, Chetti MB, Patil BS. Apoptosis-mediated proliferation inhibition of human colon cancer cells by volatile principles of Citrus aurantifolia. Food Chem 2009;114(4):1351–1358. doi:10.1016/j.foodchem.2008.11.033.
[104] Eid AM, Jaradat N, Shraim N, Hawash M, Issa L, Shakhsher M, *et al*. Assessment of anticancer, antimicrobial, antidiabetic, anti-obesity and antioxidant activity of Ocimum Basilicum seeds essential oil from Palestine. BMC Complement Med Ther 2023;23(1):221. doi:10.1186/s12906-023-04058-w, PMID:37403162.
[105] Panyajai P, Chueahongthong F, Viriyaadhammaa N, Nirachonkul W, Tima S, Chiampanichayakul S, *et al*. Anticancer activity of Zingiber ottensii essential oil and its nanoformulations. PLoS One

2022;17(1):e0262335. doi:10.1371/journal.pone.0262335, PMID: 35073347.
[106] Amirzadeh M, Soltanian S, Mohamadi N. Chemical composition, anticancer and antibacterial activity of Nepeta mahanensis essential oil. BMC Complement Med Ther 2022;22(1):173. doi:10.1186/s12906-022-03642-w, PMID:35752826.
[107] Liu Y, Zhong X, Ding Y, Ren L, Bai T, Liu M, *et al*. Inhibition of voltage-dependent potassium channels mediates cAMP-potentiated insulin secretion in rat pancreatic β cells. Islets 2017;9(2):11–18. doi:10.1080/19382014.2017.1280644, PMID:28103136.
[108] Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007;132(6):2131–2157. doi:10.1053/j.gastro.2007.03.054, PMID:17498508.
[109] Surampudi PN, John-Kalarickal J, Fonseca VA. Emerging concepts in the pathophysiology of type 2 diabetes mellitus. Mt Sinai J Med 2009;76(3):216–226. doi:10.1002/msj.20113, PMID:19421965.
[110] Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: Similarities and differences. J Diabetes Investig 2010;1(1-2):8–23. doi:10.1111/j.2040-1124.2010.00022.x, PMID:24843404.
[111] Roden M, Shulman GI. The integrative biology of type 2 diabetes. Nature 2019;576(7785):51–60. doi:10.1038/s41586-019-1797-8, PMID:31802013.
[112] Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol 2021;320(3):C375–C391. doi:10.1152/ajpcell.00379.2020, PMID:33356944.
[113] Wu CH, Huang SM, Lin JA, Yen GC. Inhibition of advanced glycation endproduct formation by foodstuffs. Food Funct 2011;2(5):224–234. doi:10.1039/c1fo10026b, PMID:21779560.
[114] Gandhi GR, Hillary VE, Antony PJ, Zhong LLD, Yogesh D, Krishnakumar NM, *et al*. A systematic review on anti-diabetic plant essential oil compounds: Dietary sources, effects, molecular mechanisms, and safety. Crit Rev Food Sci Nutr 2024;64(19):6526–6545. doi:10.1080/10408398.2023.2170320, PMID:36708221.
[115] Zarandi MH, Sharifiyazdi H, Nazifi S, Ghaemi M, Bakhtyari MK. Effects of citral on serum inflammatory factors and liver gene expression of IL-6 and TNF-alpha in experimental diabetes. Comp Clin Patho 2021;30:351–361. doi:10.1007/s00580-021-03205-4.
[116] Ataie Z, Dastjerdi M, Farrokhfall K, Ghiravani Z. The Effect of Cinnamaldehyde on iNOS Activity and NO-Induced Islet Insulin Secretion in High-Fat-Diet Rats. Evid Based Complement Alternat Med 2021;2021:9970678. doi:10.1155/2021/9970678, PMID:34335851.
[117] Sadgrove NJ, Padilla-González GF, Leuner O, Melnikovova I, Fernandez-Cusimamani E. Pharmacology of Natural Volatiles and Essential Oils in Food, Therapy, and Disease Prophylaxis. Front Pharmacol 2021;12:740302. doi:10.3389/fphar.2021.740302, PMID:34744723.
[118] Sales PM, Souza PM, Simeoni LA, Silveira D. α-Amylase inhibitors: a review of raw material and isolated compounds from plant source. J Pharm Pharm Sci 2012;15(1):141–183. doi:10.18433/j35s3k, PMID: 22365095.
[119] Kumar S, Narwal S, Kumar V, Prakash O. α-glucosidase inhibitors from plants: A natural approach to treat diabetes. Pharmacogn Rev 2011;5(9):19–29. doi:10.4103/0973-7847.79096, PMID:22096315.
[120] Wang S, Ding L, Ji H, Xu Z, Liu Q, Zheng Y. The Role of p38 MAPK in the Development of Diabetic Cardiomyopathy. Int J Mol Sci 2016;17(7):1037. doi:10.3390/ijms17071037, PMID:27376265.
[121] He X, Gao F, Hou J, Li T, Tan J, Wang C, *et al*. Metformin inhibits MAPK signaling and rescues pancreatic aquaporin 7 expression to induce insulin secretion in type 2 diabetes mellitus. J Biol Chem 2021;297(2):101002. doi:10.1016/j.jbc.2021.101002, PMID:34303707.
[122] Liadis N, Murakami K, Eweida M, Elford AR, Sheu L, Gaisano HY, *et al*. Caspase-3-dependent beta-cell apoptosis in the initiation of autoimmune diabetes mellitus. Mol Cell Biol 2005;25(9):3620–3629. doi:10.1128/MCB.25.9.3620-3629.2005, PMID:15831467.
[123] Sun J, Singh P, Österlund J, Orho-Melander M, Melander O, Engström G, *et al*. Hyperglycaemia-associated Caspase-3 predicts diabetes and coronary artery disease events. J Intern Med 2021;290(4):855–865. doi:10.1111/joim.13327, PMID:34309093.
[124] Chang L, Chiang SH, Saltiel AR. Insulin signaling and the regulation of glucose transport. Mol Med 2004;10(7-12):65–71. doi:10.2119/2005-00029.Saltiel, PMID:16307172.
[125] Alkhateeb HH, Kaplan NM, Al-Duais M. Understanding the Mechanism Underlie the Antidiabetic Activity of Oleuropein Using Ex-Vivo Approach. Rep Biochem Mol Biol 2022;11(1):146–156. doi:10.52547/rbmb.11.1.146, PMID:35765534.
[126] Wang W, Zhong X, Guo J. Role of 2-series prostaglandins in the pathogenesis of type 2 diabetes mellitus and non-alcoholic fatty liver disease (Review). Int J Mol Med 2021;47(6):114. doi:10.3892/ijmm.2021.4947, PMID:33907839.
[127] Kothari V, Galdo JA, Mathews ST. Hypoglycemic agents and potential anti-inflammatory activity. J Inflamm Res 2016;9:27–38. doi:10.2147/JIR.S86917, PMID:27114714.
[128] Chelladurai GRM, Chinnachamy C. Alpha amylase and Alpha glucosidase inhibitory effects of aqueous stem extract of Salacia oblonga and its GC-MS analysis. Braz J Pharm Sci 2018;54(1):e17151. doi:10.1590/s2175-97902018000117151.
[129] Ogunyemi OM, Gyebi GA, Saheed A, Paul J, Nwaneri-Chidozie V, Olorundare O, *et al*. Inhibition mechanism of alpha-amylase, a diabetes target, by a steroidal pregnane and pregnane glycosides derived from Gongronema latifolium Benth. Front Mol Biosci 2022;9:866719. doi:10.3389/fmolb.2022.866719, PMID:36032689.
[130] Fadimu GJ, Farahnaky A, Gill H, Olalere OA, Gan CY, Truong T. In-Silico Analysis and Antidiabetic Effect of α-Amylase and α-Glucosidase Inhibitory Peptides from Lupin Protein Hydrolysate: Enzyme-Peptide Interaction Study Using Molecular Docking Approach. Foods 2022;11(21):3375. doi:10.3390/foods11213375, PMID:36359988.
[131] Cui Y, Chen J, Zhang Z, Shi H, Sun W, Yi Q. The role of AMPK in macrophage metabolism, function and polarisation. J Transl Med 2023;21(1):892. doi:10.1186/s12967-023-04772-6, PMID:38066566.
[132] Boukhris M, Bouaziz M, Feki I, Jemai H, El Feki A, Sayadi S. Hypoglycemic and antioxidant effects of leaf essential oil of Pelargonium graveolens L'Hér. in alloxan induced diabetic rats. Lipids Health Dis 2012;11:81. doi:10.1186/1476-511X-11-81, PMID:22734822.
[133] Muhammad NO, Soji-Omoniwa O, Usman LA, Omoniwa BP. Antihyperglycemic activity of leaf essential oil of Citrus sinensis (L.) Osbeck on alloxan induced diabetic rats. Annu Res Rev Biol 2013;3(4):825–834.
[134] Al-Mijalli SH, Assaggaf H, Qasem A, El-Shemi AG, Abdallah EM, Mrabti HN, *et al*. Antioxidant, Antidiabetic, and Antibacterial Potentials and Chemical Composition of Salvia officinalis and Mentha suaveolens Grown Wild in Morocco. Adv Pharmacol Pharm Sci 2022;2022:2844880. doi:10.1155/2022/2844880, PMID:35755940.
[135] El-Soud NHA, El-Lithy NA, El-Saeed GSM, Wahby MS, Khalil MY, El-Kassem LTA, *et al*. Efficacy of Coriandrum Sativum L. essential oil as antidiabetic. J Appl Sci Res 2012;8(7):3646–3655.
[136] Boukhalfa D, Nabti B. Evaluation of the hypoglycemic and antimicrobial activities of the essential oil of Myrtus nivellei from Tamanrasset (southern Algeria). GSC Biol Pharm Sci 2023;22(2):272–279. doi:10.30574/gscbps.2023.22.2.0082.
[137] Nait Irahal I, Darif D, Guenaou I, Hmimid F, Azzahra Lahlou F, Ez-Zahra Ousaid F, *et al*. Therapeutic Potential of Clove Essential Oil in Diabetes: Modulation of Pro-Inflammatory Mediators, Oxidative Stress and Metabolic Enzyme Activities. Chem Biodivers 2023;20(3):e202201169. doi:10.1002/cbdv.202201169, PMID:36823346.
[138] Sebai H, Selmi S, Rtibi K, Souli A, Gharbi N, Sakly M. Lavender (Lavandula stoechas L.) essential oils attenuate hyperglycemia and protect against oxidative stress in alloxan-induced diabetic rats. Lipids Health Dis 2013;12:189. doi:10.1186/1476-511X-12-189, PMID:24373672.
[139] Assaggaf H, El Hachlafi N, El Fadili M, Elbouzidi A, Ouassou H, Jeddi M, *et al*. GC/MS profiling, in vitro antidiabetic efficacy of Origanum compactum Benth. essential oil and in silico molecular docking of its major bioactive compounds. Catalysts 2023;13(11):1429. doi:10.3390/catal13111429.
[140] Oboh G, Ademosun AO, Odubanjo OV, Akinbola IA. Antioxidative properties and inhibition of key enzymes relevant to type-2 diabetes and hypertension by essential oils from black pepper. Adv Pharmacol Sci 2013;2013:926047. doi:10.1155/2013/926047, PMID:24348547.
[141] Gábor M. Models of acute inflammation in the ear. Methods Mol Biol 2003;225:129–137. doi:10.1385/1-59259-374-7:129, PMID:12769482.
[142] Calixto JB, Campos MM, Otuki MF, Santos AR. Anti-inflammatory

compounds of plant origin. Part II. modulation of pro-inflammatory cytokines, chemokines and adhesion molecules. Planta Med 2004;70(2):93–103. doi:10.1055/s-2004-815483, PMID:14994184.
[143] Murakawa M, Yamaoka K, Tanaka Y, Fukuda Y. Involvement of tumor necrosis factor (TNF)-alpha in phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin edema in mice. Biochem Pharmacol 2006;71(9):1331–1336. doi:10.1016/j.bcp.2006.01.005, PMID:16487490.
[144] Karakoy Z, Cadirci E, Dincer B. A new target in inflammatory diseases: Lycopene. Eurasian J Med 2022;54(Suppl 1):S29–S33. doi:10.5152/eurasianjmed.2022.22300.
[145] Zhao Q, Zhu L, Wang S, Gao Y, Jin F. Molecular mechanism of the anti-inflammatory effects of plant essential oils: A systematic review. J Ethnopharmacol 2023;301:115829. doi:10.1016/j.jep.2022.115829, PMID:36252876.
[146] Dinarello CA. Anti-inflammatory Agents: Present and Future. Cell 2010;140(6):935–950. doi:10.1016/j.cell.2010.02.043, PMID:20303881.
[147] Miguel MG. Antioxidant and anti-inflammatory activities of essential oils: a short review. Molecules 2010;15(12):9252–9287. doi:10.3390/molecules15129252, PMID:21160452.
[148] Ascari J, de Oliveira MS, Nunes DS, Granato D, Scharf DR, Simionatto E, *et al*. Chemical composition, antioxidant and anti-inflammatory activities of the essential oils from male and female specimens of Baccharis punctulata (Asteraceae). J Ethnopharmacol 2019;234:1–7. doi:10.1016/j.jep.2019.01.005, PMID:30660710.
[149] Chen S, Chen H, Du Q, Shen J. Targeting Myeloperoxidase (MPO) Mediated Oxidative Stress and Inflammation for Reducing Brain Ischemia Injury: Potential Application of Natural Compounds. Front Physiol 2020;11:433. doi:10.3389/fphys.2020.00433, PMID:32508671.
[150] Frangie C, Daher J. Role of myeloperoxidase in inflammation and atherosclerosis (Review). Biomed Rep 2022;16(6):53. doi:10.3892/br.2022.1536, PMID:35620311.
[151] Premakumari PD, Kumaraswamy M, Sarayu MG. Anti-inflammatory potential of essential oil from Pogostemon benghalensis (Burm.F.) Kuntze. using animal models. J Adv Sci Res 2020;11(4):92–99.
[152] Li R, Yang JJ, Shi YX, Zhao M, Ji KL, Zhang P, *et al*. Chemical composition, antimicrobial and anti-inflammatory activities of the essential oil from Maqian (Zanthoxylum myriacanthum var. pubescens) in Xishuangbanna, SW China. J Ethnopharmacol 2014;158(Pt A):43–48. doi:10.1016/j.jep.2014.10.006, PMID:25448503.
[153] Lorençoni MF, Figueira MM, Toledo e Silva MV, Pimentel Schmitt EF, Endringer DC, Scherer R, *et al*. Chemical composition and anti-inflammatory activity of essential oil and ethanolic extract of Campomanesia phaea (O. Berg.) Landrum leaves. J Ethnopharmacol 2020;252:112562. doi:10.1016/j.jep.2020.112562, PMID:31954197.
[154] Otunola GA, Afolayan AJ. Chemical composition, antibacterial and in vitro anti-inflammatory potentials of essential oils from different plant parts of Moringa Oleifera Lam. Am J Biochem Biotechnol 2018;14(3):210–220. doi:10.3844/ajbbsp.2018.210.220.
[155] Sharma AD, Kaur I, Singh N. Tryptophan fluorescence spectroscopy: key tool to study protein denaturation/anti-inflammatory assay. Research & Reviews in Biotechnology & Biosciences 2021;8(1):90–94. doi:10.5281/zenodo.5118388.
[156] Acharya VV, Chaudhari. Modalities of protein denaturation and nature of denaturants. Int J Pharm Sci Rev Res 2021;69(2):19–24. doi:10.47583/ijpsrr.2021.v69i02.002.
[157] Cimonara MC. Lysosomes, lysosomal storage diseases and inflammation. J Inborn Errors Metab Screen 2016;4:1–8. doi:10.1177/2326409816650465.
[158] An BS, Kang JH, Yang H, Jung EM, Kang HS, Choi IG, *et al*. Anti-inflammatory effects of essential oils from Chamaecyparis obtusa via the cyclooxygenase-2 pathway in rats. Mol Med Rep 2013;8(1):255–259. doi:10.3892/mmr.2013.1459, PMID:23652412.
[159] Belkhodja H, Meddah B, Sidelarbi K, Bouhadi D, Medjadel B, Brakna A. In vitro and in vivo anti-inflammatory potential of Eucalyptus globulus essential oil. J Appl Biosci 2022;16(1):80–88. doi:10.5281/zenodo.5826169.
[160] Pandur E, Balatinácz A, Micalizzi G, Mondello L, Horváth A, Sipos K, *et al*. Anti-inflammatory effect of lavender (Lavandula angustifolia Mill.) essential oil prepared during different plant phenophases on THP-1 macrophages. BMC Complement Med Ther 2021;21(1):287. doi:10.1186/s12906-021-03461-5, PMID:34819075.