



## Review Article

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



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### 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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> 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.<sup>4</sup>

System biology is a unifying approach that connects cells, tis-

issues, 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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8,9</sup> 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).

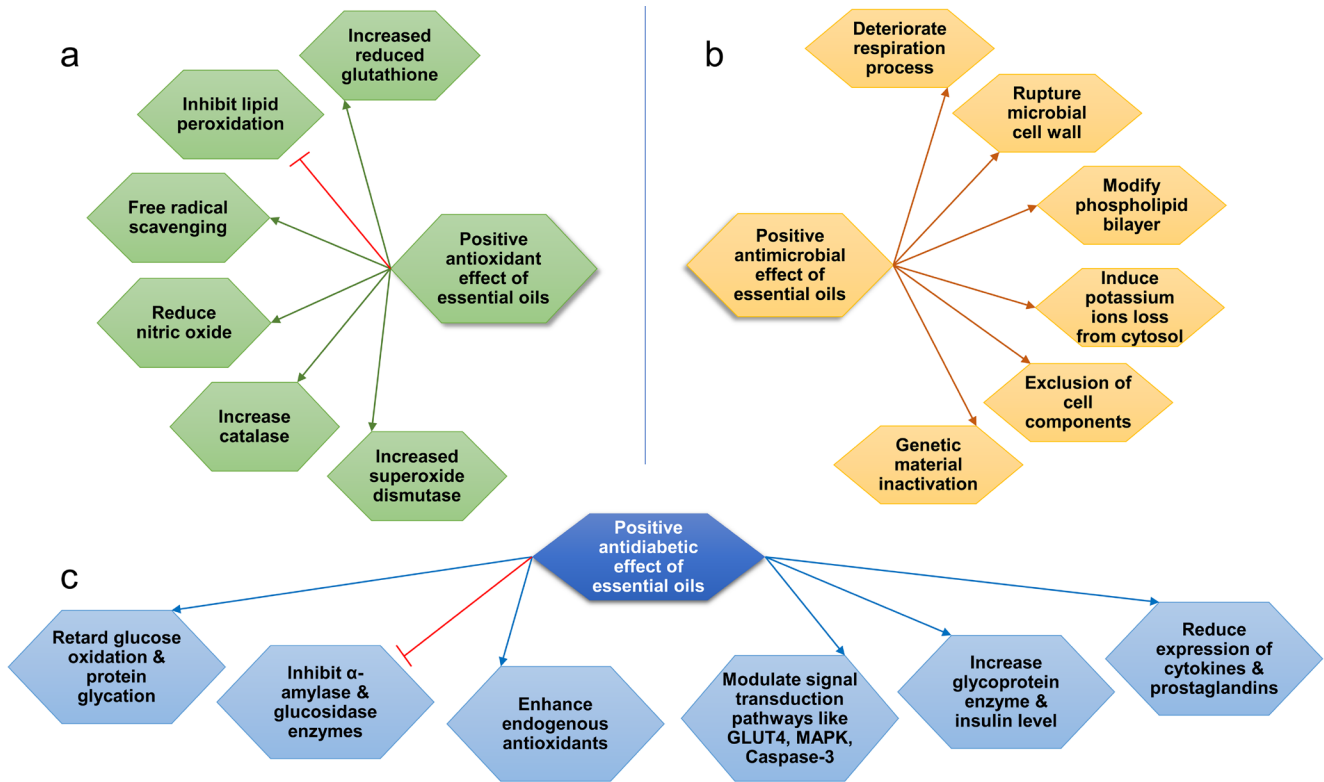
### Antioxidative activities of essential oils

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

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

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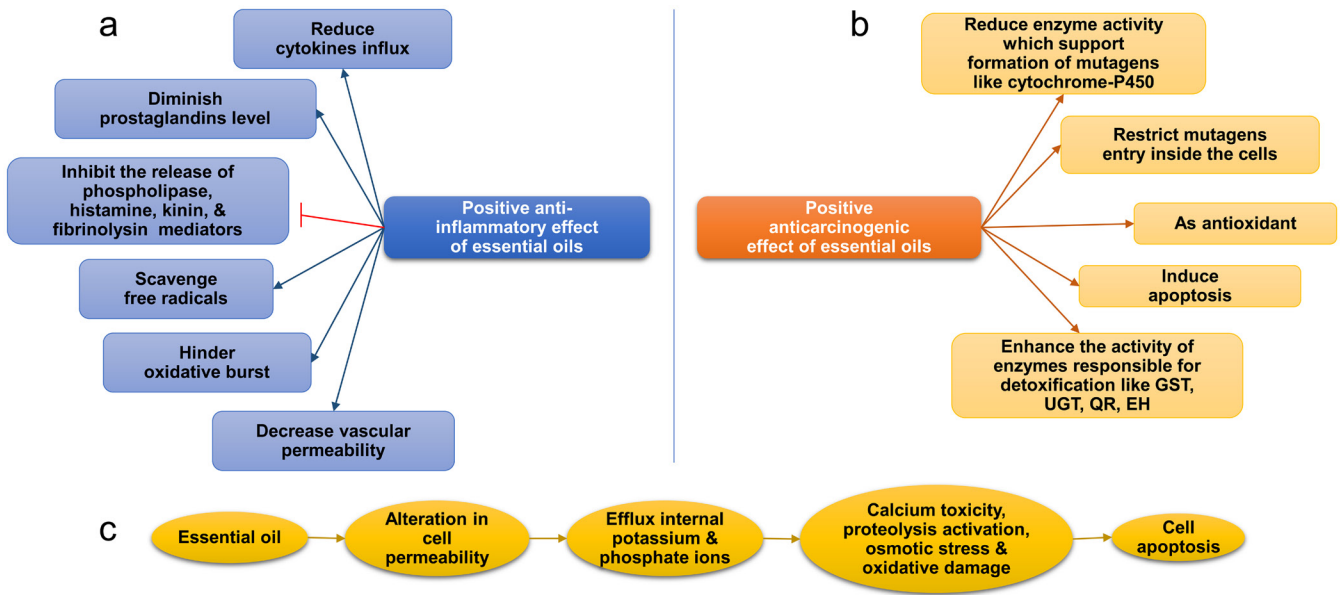
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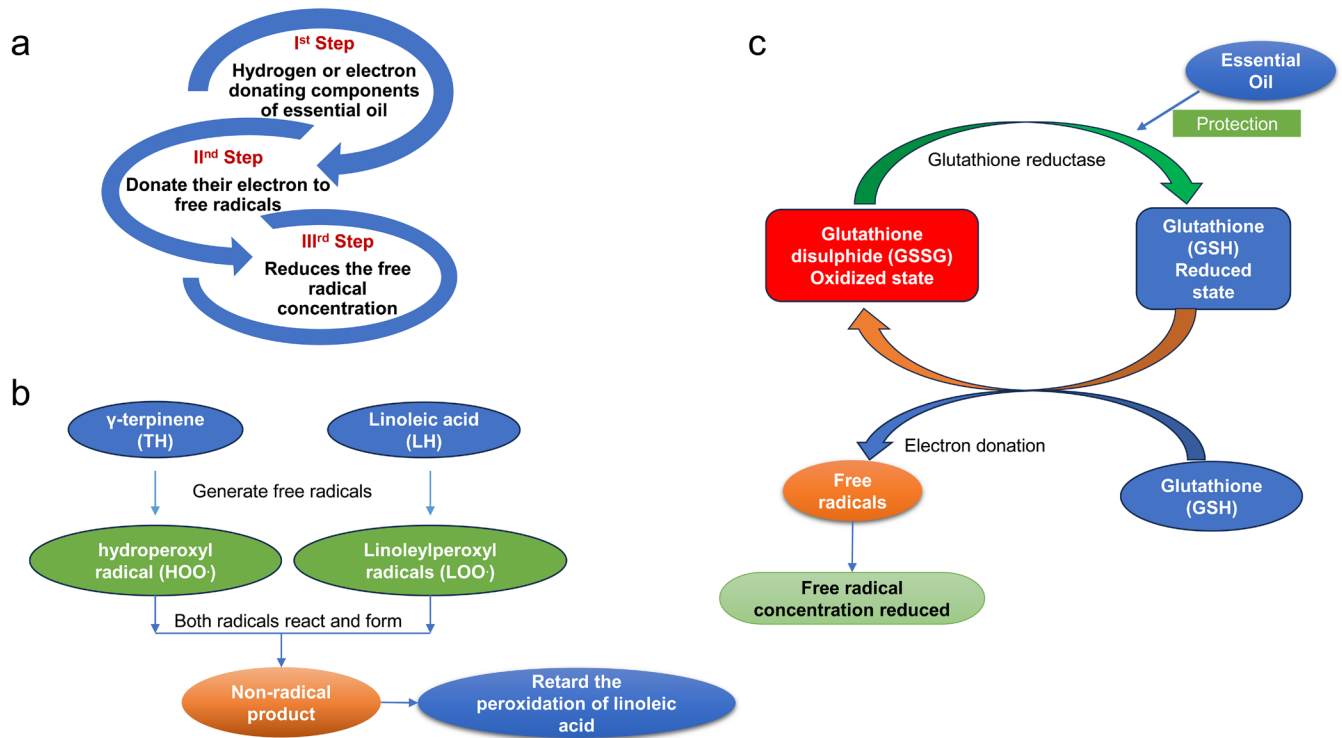
**Fig. 1. Mechanism of essential oils to control oxidative stress, microbes and diabetes.** (a) Antioxidative mechanism of essential oil. (b) Antimicrobial mechanism of essential oil. (c) Anti-diabetic mechanism of essential oil. GLUT4, glucose transporter protein type-4; MAPK, mitogen-activated protein 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.<sup>10,11</sup> 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.<sup>12,13</sup>

There are various *in vitro* approaches for the detection of the antioxidant potential of compounds. Among them Diphenylpicrylhydrazyl (DPPH) assay,  $\beta$ -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.<sup>14,15</sup>

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,<sup>16</sup> 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.<sup>17,18</sup>

**Mechanism of inhibition of lipid peroxidation by essential oils**

A monoterpene hydrocarbon,  $\gamma$ -terpinene, a component of essential oils retards the peroxidation of linoleic acid. During the chain reaction of linoleic acid linoleylperoxyl radicals generated, peroxidation of  $\gamma$ -terpinene yields hydroperoxyl radical. Both free radicals react quickly and form a non-radical product and retard the peroxidation of linoleic acid.<sup>19</sup>

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.<sup>20</sup>

In some cases, highly oxidizable components of essential oil get oxidized with the substrate and form peroxy radicals, which rapidly form non-radical products and decrease the concentration of free radicals.<sup>20</sup>

**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.<sup>21</sup> This enzyme is responsible for reducing glutathione disulfide (GSSG) to its sulfhydryl form, known as glutathione (GSH), a potent endogenous antioxidant agent.<sup>22</sup> Glutathione, chemically referred to as  $\gamma$ -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.<sup>15</sup>

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.<sup>23</sup>

Superoxide dismutase stimulates superoxide anions to hydrogen peroxide, which is later converted to water and oxygen by catalase.<sup>24</sup> 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.<sup>25</sup> The Superoxide dismutase requires a metallic catalyst for activation and provides defense against superoxide ( $O_2^{\cdot-}$ ) particularly. It is responsible for inhibiting oxidative activation of nitric oxide; thus, it protects endothelial and mitochondrial dysfunction by preventing peroxynitrite formation.<sup>26</sup>

Nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, xanthine oxidase, nitric oxide synthase (NOS), lipoxygenase, and mitochondrial enzymes generate  $O_2^{\cdot-}$ .<sup>27</sup> The generated superoxide is converted to  $H_2O_2$  by SOD. Dismutation of  $H_2O_2$  by superoxide dismutase produces hydroxyl ( $OH^{\cdot}$ ) free radicals. Superoxide-free radicals and hydroxyl-free radicals act on lipid membranes and encourage the formation of lipid radical and lipid peroxy radicals, which promote oxidative stress and cause lipid peroxidation.<sup>28</sup> 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 ( $ONOO^{\cdot}$ ).<sup>29</sup>

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.<sup>30,31</sup> 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  $\beta$ -cells from the damaging effects of hydrogen peroxide.<sup>32,33</sup>

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

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.<sup>35</sup>

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.<sup>36</sup>

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.<sup>37</sup> 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).<sup>38</sup>

#### Works that reflect the antioxidant activity of essential oils

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

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.<sup>41</sup>

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

Amiri worked on *Thymus daenensis* (*lancifolius*) Celak and *Thymus eriocalyx*. He found better scavenging effect of *Thymus daenensis* (*lancifolius*) Celak at the dose of  $19.1 \pm 0.1 \mu\text{g/mL}$  and better inhibitory lipid peroxidation effect of *Thymus eriocalyx* at the dose of  $34.2 \pm 0.4 \mu\text{g/mL}$ .<sup>44</sup> *Salvia aetheroleum* (Sage) replicates a good radical scavenging effect with  $10.5 \mu\text{L/mL}$  and effective inhibition of 15-lipoxygenase (responsible for the generation of lipid peroxides via oxidation of unsaturated fatty acids) at  $0.064 \mu\text{L/mL}$ .<sup>45</sup>

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.<sup>46</sup> *Syzygium aromaticum*,<sup>47</sup> *Nepeta ciliaris*, and *Nepeta leucophylla* showed good radical scavenging effects at  $5.76 \mu\text{g}\cdot\text{mL}^{-1}$ ,  $0.9 \pm 0.2 \text{ mg/mL}$ , and  $1.2 \pm 0.5 \text{ mg/mL}$ , respectively. *Erigeron mucronatusi*, *Erigeron annuus*, and *Nepeta leucophylla* showed better inhibitory effects on lipid peroxidation.<sup>48</sup>

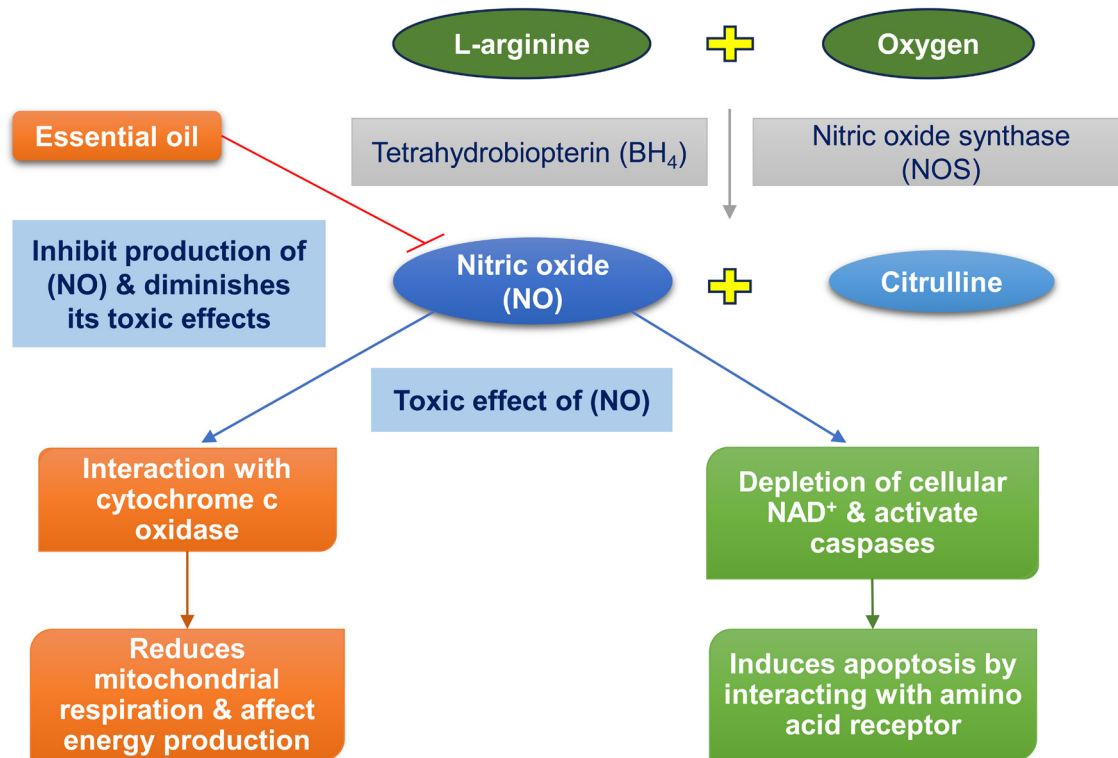


Fig. 4. Function of nitric oxide and role of essential oil.

The effective free radical scavenging effect is also shown by *Origanum compactum*, *Curcuma zedoaria* Rosc, *Eucalyptus camaldulensis* and *Phoenix dactylifera*.<sup>49-51</sup> Ozkan *et al.*<sup>52</sup> worked on *Salvia pisdica* 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.<sup>53</sup> This disrupts the cell wall structure and causes the microbial cells to shrink.<sup>54</sup> 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.<sup>55</sup> It also inhibits the activity of the enzyme ATPase and modifies the growth of bacteria. A study on the essential oil of *Cupressus funebris* revealed the exclusion of bacterial protein by rupturing the cell wall, which is responsible for the maintenance of the integrity of the cell.<sup>56</sup>

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.<sup>57</sup> 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.<sup>58,59</sup>

**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.<sup>60</sup> 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*.<sup>61</sup>

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.<sup>62</sup>

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.<sup>63</sup>

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 millimolar.<sup>64</sup> *Monarda didyma* essential oil reduces the activity of glucose-6-phosphate dehydrogenase, citrate synthase, isocitrate dehydrogenase and  $\alpha$ -ketoglutarate dehydrogenase in Carbapenem-resistant *Klebsiella pneumoniae*. It also inhibits biofilm formation, damages cell membrane structure, and inhibits energy metabolism.<sup>65</sup>

### 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.<sup>66,67</sup> 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.<sup>68</sup>

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.<sup>69</sup>

### 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<sub>450</sub>.<sup>70,71</sup> They act as a detoxifying agent via enhancing the activity of enzymes responsible for detoxification like glutathione S-transferase (GST),<sup>72</sup> uridine-5'-diphosphoglucuronosyltransferase, quinone reductase (QR) and epoxide hydrolase.<sup>73-75</sup> It worked as an antioxidant agent by protecting the oxidative impairment of cells through increasing endogenous antioxidant enzymes like GSH, SOD, catalase, and GPx.<sup>14</sup> It also acts as an anti-proliferative agent and induces apoptosis by a) changing the mitochondrial membrane barrier, b) increasing reactive oxygen species, c) decreasing internal glutathione level,<sup>76,77</sup> 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.<sup>78-80</sup>

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.<sup>81</sup>

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.<sup>82</sup> These enzymes act as meta-

bolic 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.<sup>83</sup>

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.<sup>84</sup> 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.<sup>85,86</sup> In some cases, these glutathione conjugates get more reactive and form episulfonium intermediates, which are responsible for DNA modification.<sup>87</sup> 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.<sup>88</sup>

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.<sup>89</sup> It is an important enzyme of glucuronidation (detoxification mechanism of the body), responsible for the biotransformation of carcinogens that enter into the body through diet or as pollutants from the air.<sup>90</sup> In the bladder, acidic urine is responsible for the hydrolysis of glucuronide-carcinogen to release ultimate carcinogens.<sup>91,92</sup>

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.<sup>93</sup> 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).<sup>94</sup>

### 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.<sup>95</sup> 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.<sup>96</sup> 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<sub>50</sub> 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.<sup>97</sup>

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

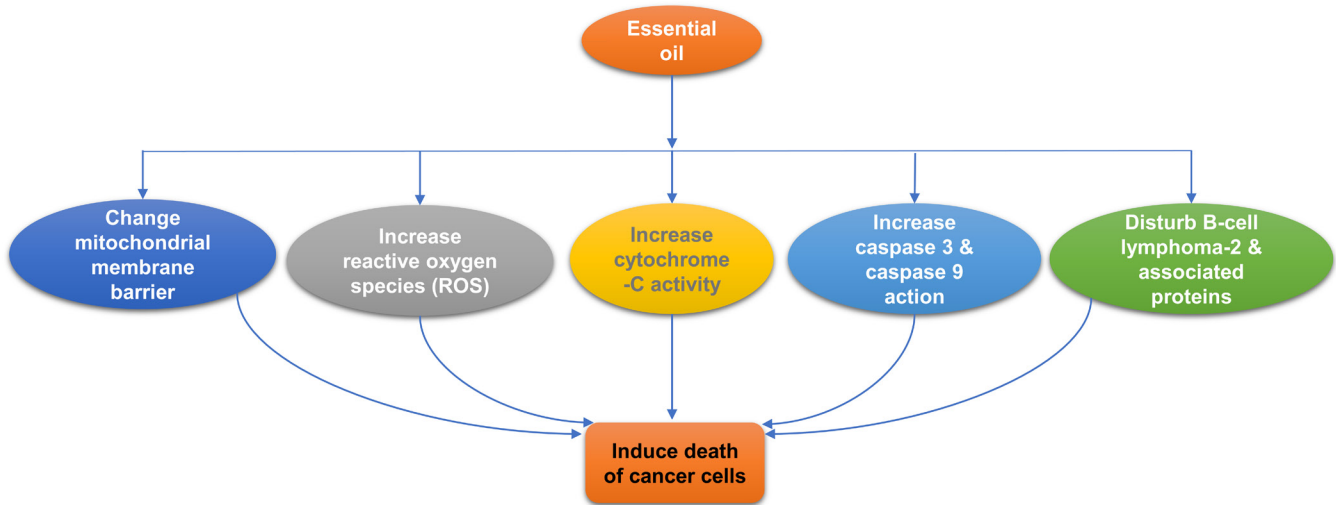


Fig. 5. Mechanism of induction of cancer cells death by essential oils.

cellular network formation, induces cancer cell death and cessation of multicellular tumor spheroids.<sup>98</sup> *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.<sup>99</sup> *Commiphora gileadensis* essential oil exhibited anti-proliferative and proapoptotic effects through DNA “ladder” and caspase-3 activation in cancer cell lines.<sup>100</sup> *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.<sup>101</sup>

*Rosmarinus officinalis* essential oil exhibited dose-dependent cytotoxicity (inhibition of cell proliferation) against human breast adenocarcinoma (MDA-MB-231) cells with IC<sub>50</sub> value at 59.35 µg/mL.<sup>102</sup> *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.<sup>103</sup>

*Ocimum basilicum* essential oil found good anticarcinogenic

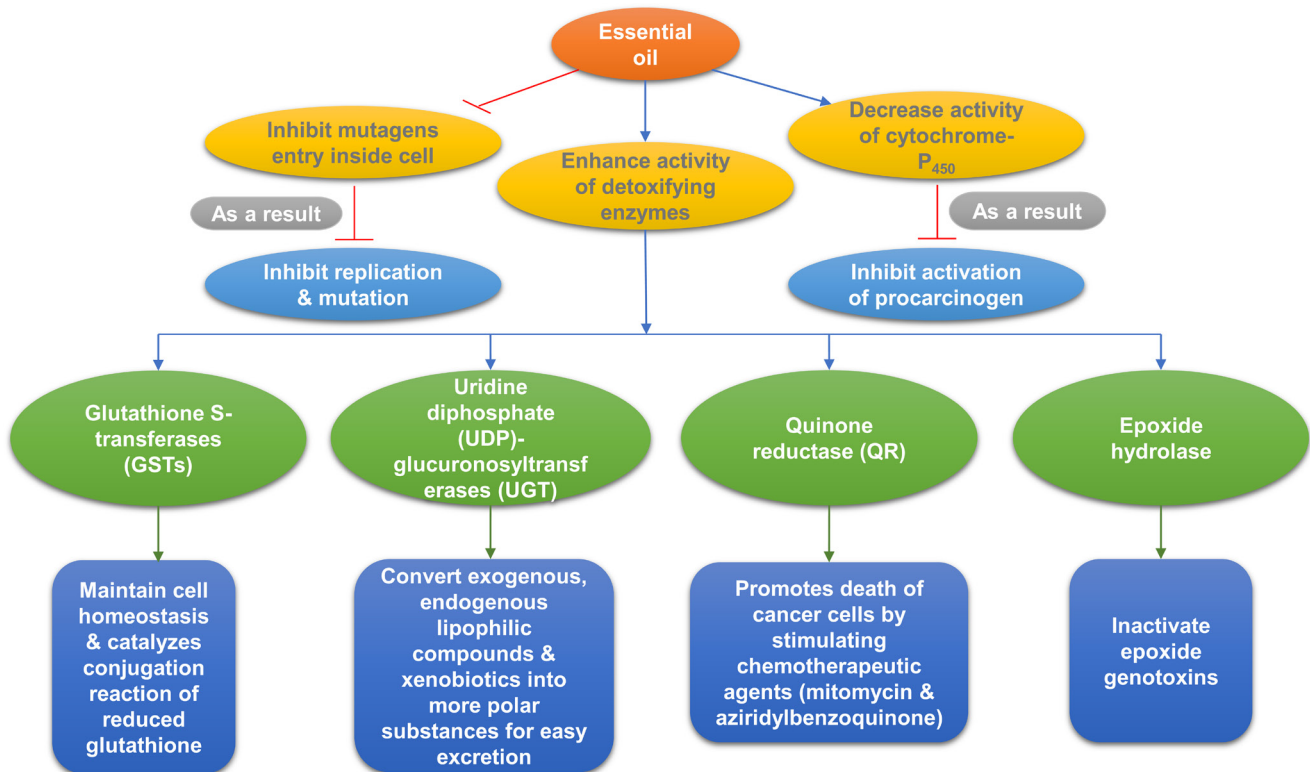


Fig. 6. Antimutagenic and detoxifying mechanism of essential oil.

activity against human liver adenocarcinoma cell lines (Hep3B) at  $56.23 \pm 1.32$   $\mu\text{g/mL}$  and human breast cancer cell lines (MCF-7) at  $80.35 \pm 1.17$   $\mu\text{g/mL}$ .<sup>104</sup> Essential oil of *Zingiber ottensii* plants showed 50% minimum inhibitory activity against human lung cancer cells (A-549) at  $43.37 \pm 6.69$   $\mu\text{g/mL}$ , human breast cancer cell lines (MCF-7) at  $9.77 \pm 1.61$   $\mu\text{g/mL}$ , human cervix carcinoma cell line (HeLa) at  $23.25 \pm 7.73$   $\mu\text{g/mL}$  and myelogenous leukemia cell lines (K562) at  $60.49 \pm 9.41$   $\mu\text{g/mL}$ .<sup>105</sup>

*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.<sup>106</sup>

#### 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.<sup>107</sup>

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.<sup>108-110</sup>

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- $\alpha$  (TNF- $\alpha$ ) and interleukins (IL-6 and IL-1 $\beta$ ), known as metabolic inflammation, which plays a significant part in insulin-resistant and type-2-diabetes mellitus subsequently.<sup>111,112</sup>

#### 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.<sup>113</sup> 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.<sup>114</sup> They significantly reduce the expression of TNF- $\alpha$ , IL-1 $\beta$ , IL-4, IL-6, iNOS and cyclooxygenase 2 (COX-2).<sup>115,116</sup> Essential oils increase insulin levels, glycoprotein enzymes, enhance endogenous antioxidant enzymes like SOD, catalase, and GPx, reduce glutathione and vital glycolytic enzymes.<sup>117</sup> Essential oils inhibit  $\alpha$ -amylase and glucosidase enzymes, which catalyze carbohydrate metabolism, thus retard glucose release and absorption and, in turn, suppress postprandial hyperglycemia.<sup>118,119</sup>

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.<sup>120,121</sup> Caspase 3 activity plays a crucial role in  $\beta$ -cell apoptosis, which reduces insulin production. Altering or diminishing caspase 3 effects can decrease  $\beta$ -cell apoptosis and maintain insulin levels.<sup>122,123</sup> 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.<sup>124,125</sup>

Hepatic PGF $2\alpha$  (prostaglandin F  $2\alpha$ ) 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 $_2$  (Prostaglandin I  $2$ /Prostacyclin) also induce gluconeogenesis and induces insulin resistance.<sup>126</sup> 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- $\alpha$ , IL-6 and IL-1 $\beta$ ) leading to chronic inflammation and hyperglycemia. Thus, inhibition of prostaglandins and cytokines retards insulin resistance, enhances glycoprotein enzymes, and raises insulin levels.<sup>127</sup>

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

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).<sup>131</sup>

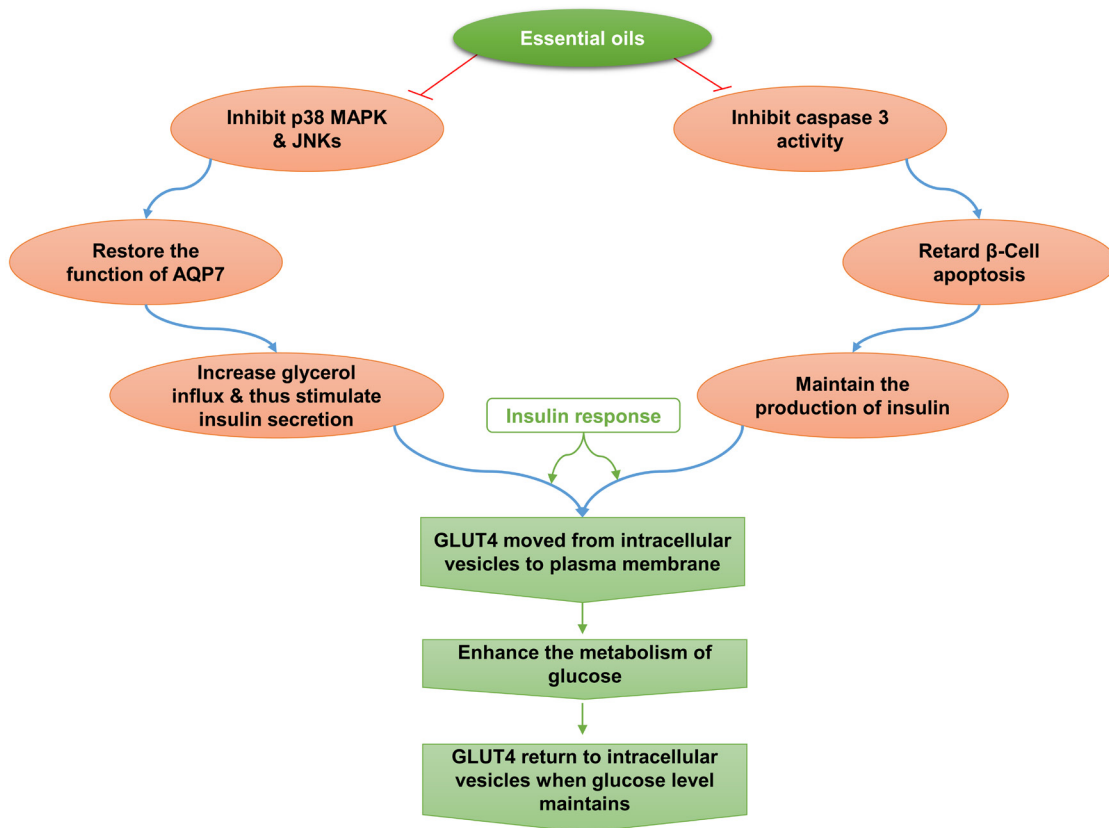
#### Works that reflect the anti-diabetic activity of essential oils

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.<sup>132</sup> 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.<sup>133</sup>

Essential oils of *Salvia officinalis* and *Mentha suaveolens* showed inhibitory effects on  $\alpha$ -amylase and  $\alpha$ -glucosidase.  $\alpha$ -amylase inhibition was obtained at  $81.91 \pm 0.03$   $\mu\text{g/mL}$  (IC $_{50}$  value) and  $94.30 \pm 0.06$   $\mu\text{g/mL}$  (IC $_{50}$  value), and  $\alpha$ -glucosidase inhibition was obtained at  $113.17 \pm 0.02$   $\mu\text{g/mL}$  (IC $_{50}$  value) and  $141.16 \pm 0.2$   $\mu\text{g/mL}$  (IC $_{50}$  value) by *Salvia officinalis* and *Mentha suaveolens* respectively.<sup>134</sup> *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  $\beta$ -cells, it improves insulin secretion and helps to reduce blood glucose levels.<sup>135</sup> *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.<sup>136</sup>

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

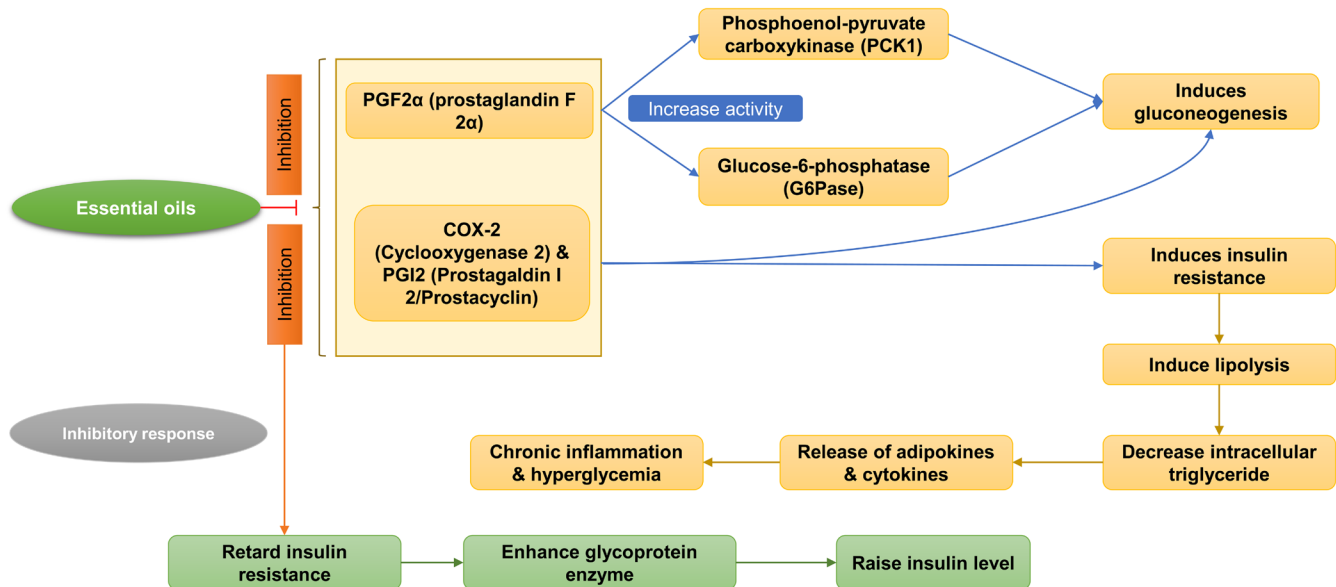




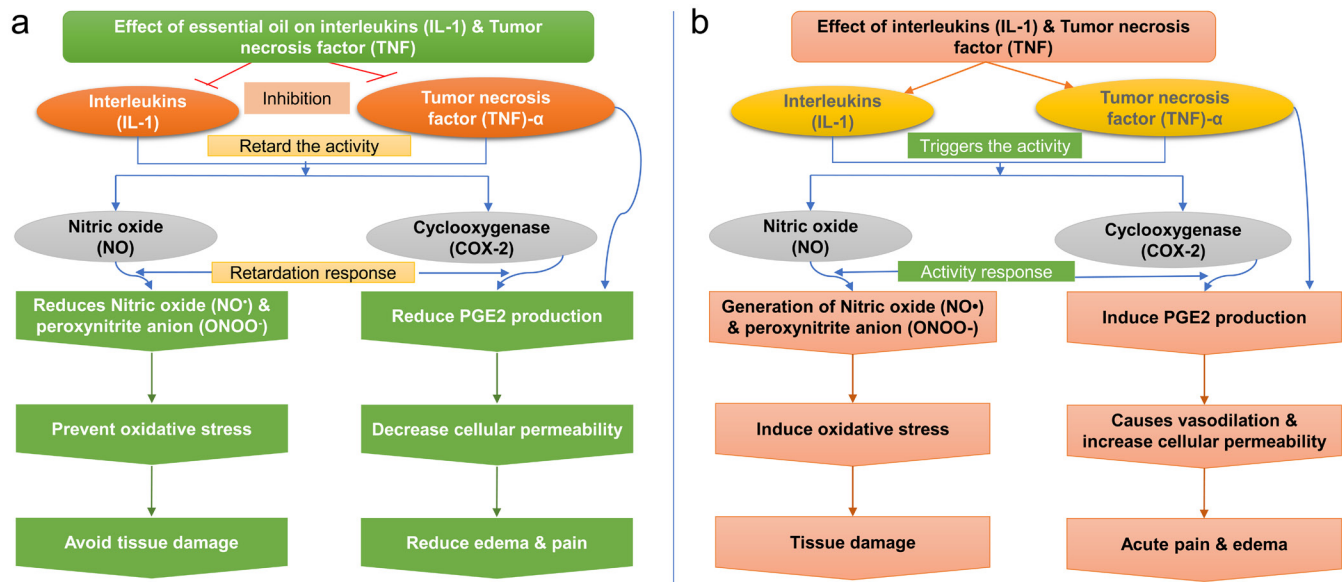
**Fig. 7. Anti-diabetic mechanism of essential oils through signaling pathways.** AQP, aquaporin; GLUT4, glucose transporter protein type-4; JNKs, jun amino-terminal kinases; MAPK, mitogen-activated protein kinase.

abolic enzymes in streptozotocin-induced diabetic rats. Additionally, it successfully inhibited  $\alpha$ -amylase.<sup>137</sup> *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.<sup>138</sup>



**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  $\alpha$ -amylase and  $\alpha$ -glucosidase. Carvacrol and thymol, components of essential oil, showed the best binding affinity towards the enzymes and modulated their activities.<sup>139</sup> Black pepper essential oil showed stronger inhibition against  $\alpha$ -glucosidase than  $\alpha$ -amylase. It alters the blood glucose level by reducing starch catabolism.<sup>140</sup>

**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.<sup>141-143</sup>

**Anti-inflammatory mechanism of essential oils**

Cytokine is a group of pro-inflammatory interleukins (IL-1- $\beta$ , TNF- $\alpha$ , IL-6, IL-15, IL-17, and IL-18), anti-inflammatory interleukins (IL-4, IL-10, and IL-13), interferon- $\gamma$ , TNF- $\alpha$ . TNF- $\alpha$  is responsible for vasodilation and increase of vascular permeability, which leads to systemic edema.<sup>144</sup> Leukotriene B4 encourages macrophage degranulation and activated neutrophils to produce superoxide. The excess amount of superoxide damages tissues via oxidative stress by reducing the activation and proliferation of T lymphocytes.<sup>145</sup> 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,

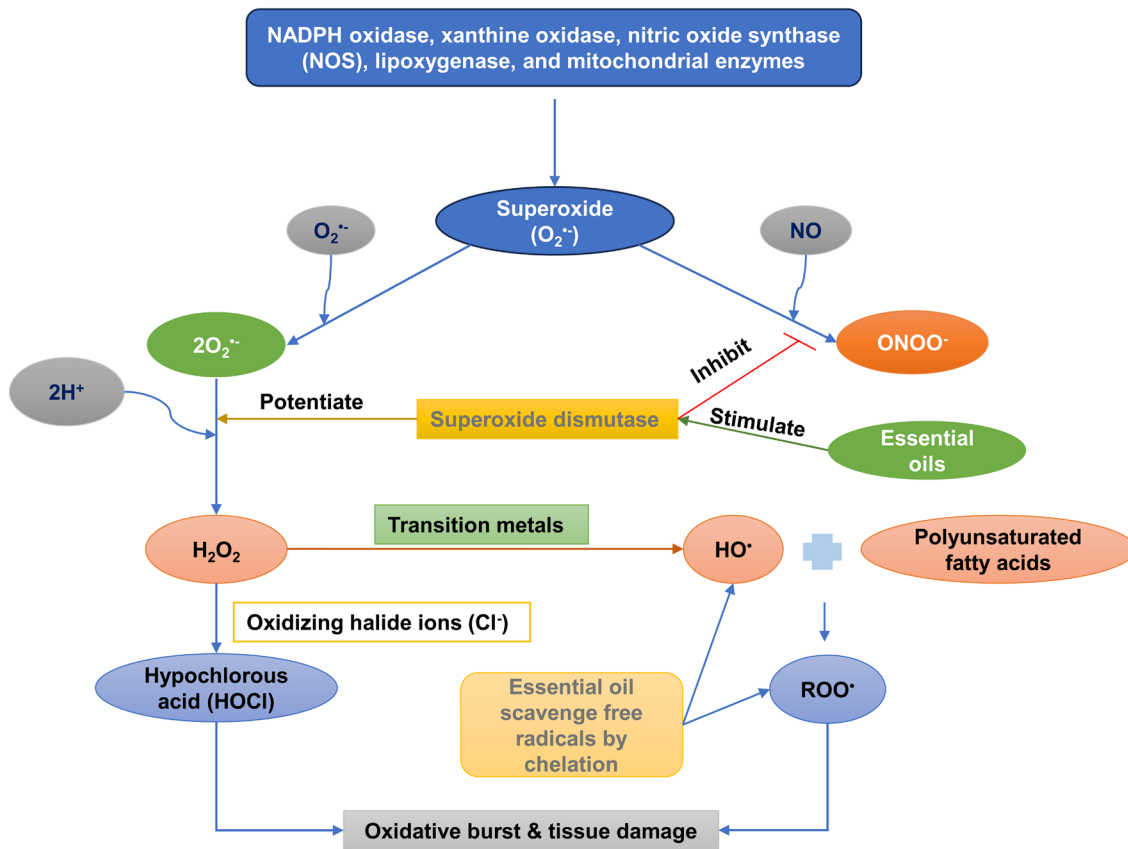
where they activate neutrophils and produce inflammation, loss of functioning, and tissue damage. IL-8 also activate neutrophils, leading to degradation of tissues. The anti-inflammatory interleukins (IL-4, IL-10, and IL-13) and transforming growth factor- $\beta$  conquer the synthesis of IL-1, TNF, 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.<sup>146</sup> The excess production of nitric oxide generates nitric oxide (NO) and peroxynitrite anion (ONOO<sup>-</sup>) 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<sub>2</sub><sup>-</sup>). 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 peroxy 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- $\kappa$ B (NF- $\kappa$ B), ultimately leading to the modulation of inflammatory responses (Fig. 10).<sup>147</sup>

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.<sup>148</sup> 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<sup>-</sup>, peroxynitrite anion; ROO<sup>•</sup>, peroxy radicals.

oxidative activity,<sup>149</sup> 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.<sup>150</sup>

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.<sup>151</sup>

*Zanthoxylum myriacanthum* var. *pubescens* Huang essential oil inhibited nitric oxide production in dose-dependent manner in LPS-induced RAW 264.7 cells.<sup>152</sup> *Campomanesia phaea* essential oil gives a marked decrease in the production of IL-6, TNF- $\alpha$ , NO, superoxide radical, and NF- $\kappa$ B activity when assayed for anti-inflammatory activity.<sup>153</sup>

*Moringa oleifera* Lam essential oil protects proteins from denaturation and maintains the stability of the membrane.<sup>154</sup> Protein denaturation is a biochemical process that disrupts the hydrogen, hydrophobic, and disulfide bonds, which leads to alteration in the structure of the protein.<sup>155</sup> 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.<sup>156</sup> Lysosomal enzymes produce autoantigens, alter the mucosal barrier, and increase cytokine secretions.<sup>157</sup>

*Chamaecyparis obtuse* essential oil inhibited the expression of cyclooxygenase, reduced the production of PGE<sub>2</sub>, and diminished the expression of TNF- $\alpha$  when assayed for anti-inflammatory effect.<sup>158</sup> *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  $\mu$ g/mL.<sup>159</sup> The essential oil of *Lavandula angustifolia* Mill flowers of the beginning stage significantly reduces interleukins IL-1, IL-8, and NF- $\kappa$ B.<sup>160</sup>

### 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, anti-diabetic, 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.

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## Conflict of interest

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

## Author contributions

RK is the sole author of the manuscript.

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