

A Review on Non-polyphenolic and Terpenoid Phytoconstituents with Antioxidant and Cytotoxic Potential

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons)

Department of Pharmacy
Brac University
March 2020

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:



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Approval

The thesis titled “A Review on Non-polyphenolic and Terpenoid Phytoconstituents with Antioxidant and Cytotoxic Potential” submitted by Kazi Zeba Ahmed (15146043) of Spring, 2015 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) on 2nd of March, 2020

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Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

Plants with antioxidant and cytotoxic activity possess wide number of different phytoconstituents such as tocopherol, polyphenolic compounds, flavonoids, ascorbic acid etc. However, plants having non-polyphenolic compounds and terpenoids play a vital role in treating free radical induced diseases and cancer. The aim of this review was to compile all possible non-phenolic compounds and terpenoids with promising antioxidant properties and cytotoxicity so that future scientists can focus on these compounds to further investigate their potential to treat Alzheimer's diseases, aging, and cancer. The required information for this review work had been accumulated by using valid sources such as PubMed, Science direct, google scholars etc. In this review, it has been presented that non-polyphenolic compounds and terpenoids have various beneficial effects such as anticancer, anti-microbial, anti-inflammatory etc. Further investigations of these compounds may help to facilitate the discovery of new drugs for treating patients having different kinds of diseases.

Keywords: Non-phenolic; Antioxidant; Terpenoids; Cytotoxicity; Cancer

Dedication

Dedicated to my parents and to my thesis supervisor, Dr. Raushanara Akter

Acknowledgement

First of all, I want to thank Almighty Allah for giving me the strength and dedication to finish the project and to overcome all the obstacles that accompanied with it. It would not have been possible to accomplish the purpose of the work without His mercy.

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List of Acronyms

DNA	Deoxyribonucleic Acid
UV	Ultra Violet
GERD	Gastro Esophageal Reflux Disease
ROS	Reactive Oxygen Species
DPPH	Diphenyl Picryl Hydrazyl
BBB	Blood Brain Barrier

Chapter 1

Introduction

1.1 What is Anti-oxidant?

From the very beginning, it can be observed that various natural products or bioactive compounds are used vigorously in food supplements, medicines, nutrient supplements etc. Basically their various beneficial effects like antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, anti-necrotic, neuroprotective are the main reasons behind showing their effectiveness for preventing different human diseases (El-Sayed et al., 2008). However, various bioactive compounds such as phenolic, non-phenolic, flavonoids, terpenoids, and saponins can be extracted from various sources amongst which, plant sources are highly preferable (vegetable, fruit etc.)

Antioxidants are mainly the substances having protection ability against free radical cell damages. In medical science oxidation basically refers to a chemical reaction in which oxygen loses its electron and chain sequences hence producing free radicals (reactive substances produced continuously by metabolic processes), that may damage the cells of organisms, proteins and DNA (Haustein, 2014).

Considering the health effect of natural antioxidants, which is mainly, derived from food and medicinal plant and this is also from industrial agricultural by-products. Antioxidants those derived from plants are identified as polyphenols in which phenolic acid, flavonoids, lignin, tannins etc. are included. From the enormous list of the plant antioxidants, the non-polyphenolic compounds and terpenoids are focused here for their huge range of biological activities including antioxidant characteristics (Xu et al., 2017).

1.2 Free Radical Generation

The main balance between anticancer and free radicals generates various human disease such as cancer, aging, Alzheimer's disease, Parkinson's disease, cardiovascular disease, liver damage, diabetes, inflammatory joint diseases, atherosclerosis etc. For example, in cancer, anomalous free radicals resulting in body is caused by toxin exposures and ionizing radiation (Singh et al., 2016) (Pham-Huy et al., 2008). Degenerative diseases which are caused by free radicals are basically categorize by some diseases given below-

- Neoplasm- tumor, cancer etc.
- Endocrine disease- Thyroidism
- Disease of nervous system
- Blood diseases
- Skin diseases
- Respiratory system diseases
- Eye diseases
- Ear diseases
- Medical induced- radiotherapy, chemotherapy etc.
- Neuro-depression.
- Ischemia-heart attack and organ transplant.
- Aging- wrinkles, freckles
- Inflammation- rheumatoid arthritis, wounds etc.

- Stress induced
- Metabolic syndrome- diabetes, hypertension, obesity etc. (Pham-Huy et al., 2008) (Hajhashemi et al., 2010).

Basically free radical chain reactions, which may lead to cell damages and it can alter the addition or removing from the cell which actually change the main structure of a lipid and it may be mutated and grow tumor. Too many free radicals or too many cell damages may cause oxidative stress as it is associated with nucleic acid, lipid and proteins and plays role in disrupting those diseases (Uttara et al., 2009)

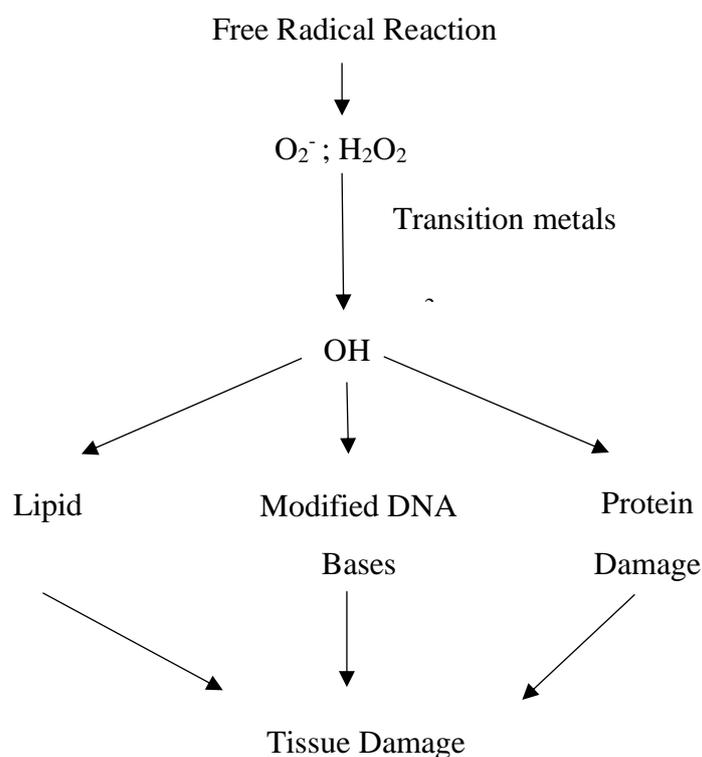


Figure 1: The consequences of free radical damage (Young & Woodside, 2001)

In free radical generation, there are some endogenous and environmental sources to trigger the formation. Endogenous sources including mitochondrial leak, respiratory burst, enzyme reaction and auto oxidation reaction. On the other hand, environmental sources such as

cigarette smoke, pollutants, UV light, ionizing radiation, xenobiotic etc. are there to introduce as one of the influencing factors.

There are various *in vitro* studies showing that various dietary antioxidants, such as ascorbic acid (vitamin c), alpha tocopherol (vitamin E), β -carotene, and flavonoids, act as effective antioxidants in biological systems such as plasma, lipoproteins, and cultured cells (Hernández-López et al., 2016).

In order to prevent these free radical diseases, first thing to keep in mind that free radical content is high in nutrient-poor meals, which is deficient of antioxidants. Some cautions like limiting highly glycemic foods, limiting red meats, limiting processed meats, limiting alcohol, avoiding volatile chemicals exposures, avoiding air pollution, prohibition on reusing cooking oils are taken to having a healthy food menu to get rid from free radicals. On the other hand, long-term consumption of foods rich in antioxidants can retard these diseases to occur (M. K. Park et al., 2016).

1.3 Classification

Antioxidant may be both endogenous and exogenous in human body. The general classification of antioxidants varied to enzyme, protein, hormones and small molecules in which phenolic compounds, non-phenolic compounds, terpenoids, carotenoids, uric acid etc. are included. It is classified into two major groups- enzymatic and non-enzymatic. The other classes of dietary antioxidants ingested through diet as like as its defense system (Huang et al., 2005).

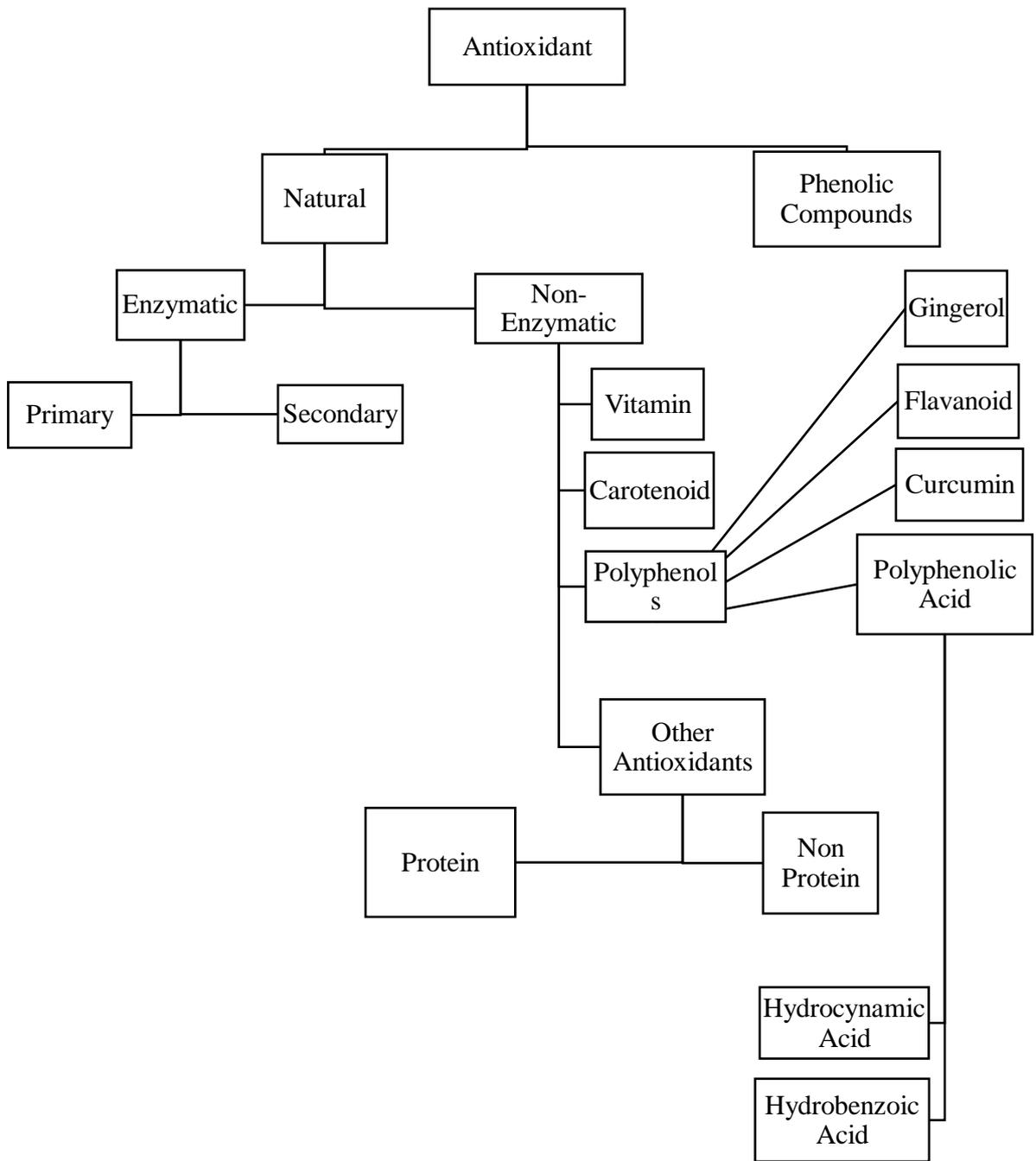


Figure 2: Classification of antioxidants (Mamta et al., 2014)

Antioxidant mechanism: Antioxidants defense in several ways, including breaking free radical chain reaction, chelating metallic compounds, hunting peroxidation producing molecules, decreasing oxygen concentration etc. these all mechanisms don't serve in same ways or it can be said that they vary in reaction to reaction. For example, flavonoids are very powerful in chelating metals as well as trapping free radicals, whereas phenolic compounds are only useful for free radical trapping. In addition, there is no single general method of antioxidant as it follows several mechanisms (Badarinath et al., 2010).

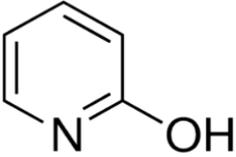
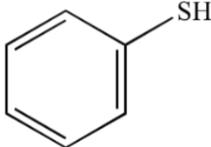
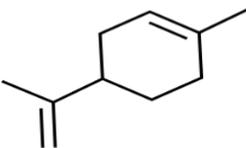
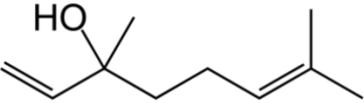
1.4 Antioxidant Compounds

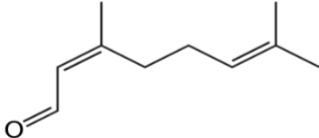
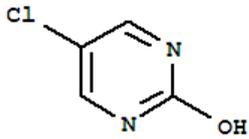
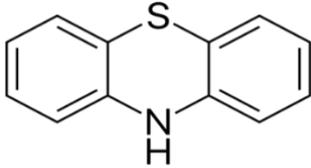
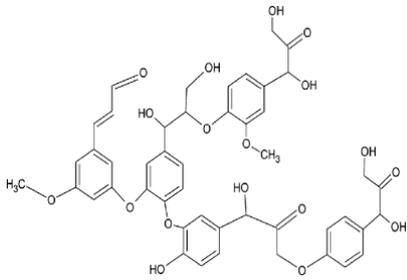
Vitamin, mineral, hormones, terpenoids, polyphenolic compounds (flavonoids, polyphenolic acids, non-flavonoid phenolic and other compounds like bilirubin, capsaicin, citric acid, oxalic acid) are categorized into antioxidant group (Tungmunnithum et al., 2018).

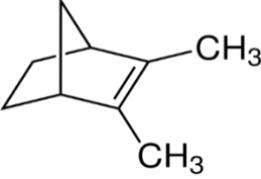
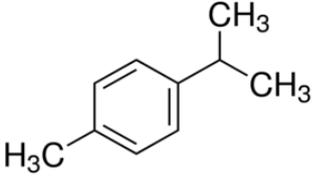
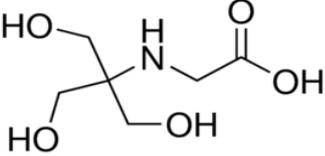
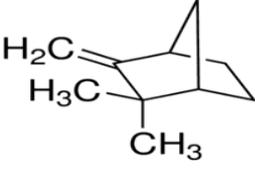
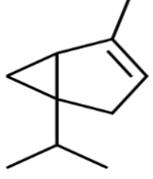
Non-polyphenolic are the organic compounds having hydroxyl group attaching with a carbon in its aromatic structure. It is an acidic derivative, which is crystalline in nature. Despite of its poisonousness, it exerts some beneficial effects like antiangiogenic activities, cytotoxicity, antifungal activity, anti-inflammatory etc (Foti & Amorati, 2009).

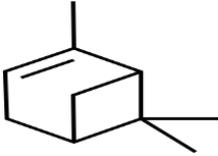
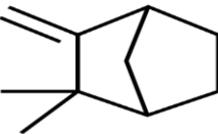
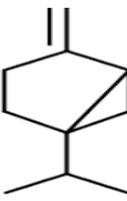
Terpenoids: It is also known as iso-prenoids is included into a large family of natural product both into primary and secondary metabolism but secondary metabolism is mostly responsible (Kawada et al., 2010). Terpenoids are classified into monoterpenoids, sesquiterpenoids, diterpenoids, sesterpenoids, and triterpenoids. However, it plays a significant role in plant by giving protection against various interspecies.

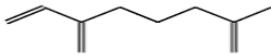
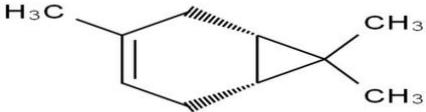
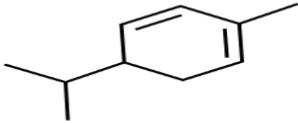
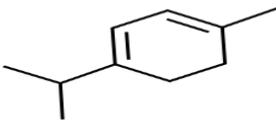
In various studies, non-polyphenolic antioxidants (Foti & Amorati, 2009) and terpenoids (Graßmann, 2005) are great supplements of degenerative diseases. Few non-polyphenolic compounds and terpenoids with few of their tests are given below-

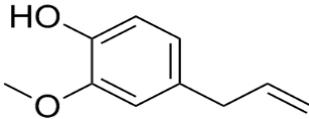
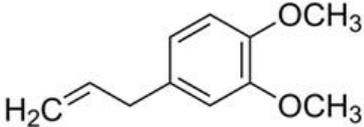
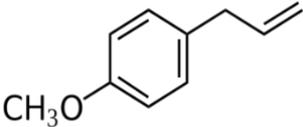
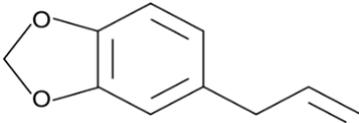
Compounds	Previously done Bioactivity studies	Structures
Pyridinols	1. Antiangiogenic activities. 2. Biological evaluation for breast cancer	
Thiols	1. Homeostasis operating diabetic neuropathy 2. Spectrophotometric Determination of Phenolic Antioxidants in the existence of Thiols and Proteins.	
Limonene	1. Antioxidants and antigenotoxic properties 2. Gastroesophageal reflux disease (GERD): analysis of conventional and alternative treatments. 3. Microbiological test	
Linalool	Antioxidant activity of linalool in patients having carpal tunnel syndrome.	

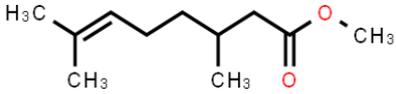
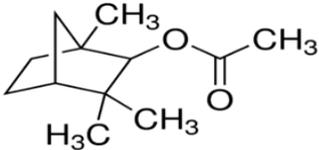
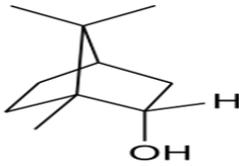
Citral	Cytotoxic effects on tumor cells, antimicrobial-antioxidants- antitumor activity,	
Pyrimidinols	Cytoprotective properties	
Phenothiazines	<p>1.The potency of Diarylamine Radical Trapping Antioxidants</p> <p>2. Design, synthesis, in vitro analysis and preliminary SAR studies</p>	
Lignin	<p>1. As an antioxidant scaffold for the growth of neuron cell and Schwann cell.</p> <p>2. Structural elucidation and antioxidant activity outlying from rice straw</p>	

Terpenoids	Tests done	Figure
Santene	1. Effect of Regular Exercise and working Beverages on Changes in Body Weight 2. Calculating of the melatonin suppression index through yellow-tinted and clear intraocular lenses.	
p-cymene	1. Chemical Composition and Antibacterial Activity 2. Synergistic effects found In vitro studies	
Tricine	The synthesis, physiochemical and biological evaluation.	
α fenchene	Essential oils chemical composition and antioxidant activities	
α -thujene	Essential oils chemical composition and antioxidant activities	

<p>α pinene</p>	<p>In vitro assessment of cytogenetic and oxidative effects</p>	
<p>Comphene</p>	<p>Comparative analysis of the Chemical Composition, Antimicrobial Activities and Antioxidant of the Volatile Oils of Hawk Tea from Six Botanical Origins.</p>	
<p>Sabinene</p>	<p>1. Identification of highly productive antitrypanosomal compounds lying into essential oils from the Apiaceae family. 2. Chemical composition, antioxidant, anti-inflammatory and anti-proliferative characteristics of essential oils</p>	

<p>Myrcene</p>	<p>1. Traversing the pro-apoptotic, anti-proliferative, and antioxidant properties</p> <p>2. Evaluation of the anti-inflammatory, anti-catabolic and pro-anabolic effects</p>	
<p>δ-3-carene</p>	<p><u>Antioxidant and antibacterial activities of crude extracts and essential oil</u></p>	
<p>Phellandrene</p>	<p>1. Exploring the anti-proliferative, pro-apoptotic, and antioxidant properties</p> <p>2. Identification of highly productive antitrypanosomal compounds</p>	
<p>Terpinene</p>	<p>1. Essential Oil Composition and Biological Activity</p> <p>2. Identification of highly effectual antitrypanosomal compounds in essential oils</p>	

Eugenol	<p>1.The effectiveness of eugenol against cisplatin-induced ototoxicity</p> <p>2.Design, Evaluation And Antimicrobial Activity</p>	
Methyl eugenol	Essential oil composition, antioxidant capacity and antifungal activity	
Estragole	<p>1.In vitro toxicity evaluation</p> <p>2.Chemometric differentiation and Classification of Some Essential Oils</p>	
Safrole	<p>1.Mode of action based risk assessment</p> <p>Essential oils: in vitro activity in opposition of Leishmania amazonensis, cytotoxicity and chemical composition</p>	

<p>Methyl citronellate</p>	<p>1. Identification of genes and proteins necessary for catabolism of acyclic terpenes and leucine/isovalerate in <i>Pseudomonas aeruginosa</i>.</p> <p>2. Identification of unique citrus chemotypes and new volatile molecules.</p>	 <p>The structure shows a 10-carbon chain with a methyl group at C1, a double bond between C2 and C3, a methyl group at C6, and a methyl ketone group at C10.</p>
<p>Fenchyl acetate</p>	<p>1. Chemical and biological characterization</p> <p>2. Fumigant toxicity and oviposition deterrence</p>	 <p>The structure shows a bicyclic monoterpene core with three methyl groups and an acetate group attached to one of the ring carbons.</p>
<p>D-borneol</p>	<p>Chemical composition and larvicidal effects of essential oil of <i>Blumea martiniana</i></p>	 <p>The structure shows a bicyclic monoterpene core with a hydroxyl group and two methyl groups attached to the rings.</p>

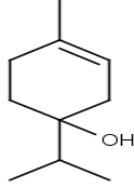
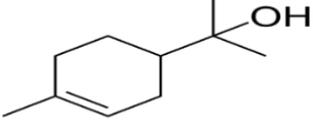
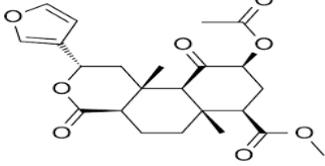
Terpinene-4-ol	<p>1. Chemical Composition and Antimicrobial Activity</p> <p>2. Anticonflict effects of lavender oil and identification of its active constituents.</p>	
α terpineol	<p>1. Antimicrobial and antioxidant properties of hydrocarbon and oxygenated monoterpenes opposed to some foodborne pathogens through in vitro and in silico studies.</p> <p>2. Chemical Composition and Biological Activity</p>	
Camphor	Searching for cytotoxic compounds against ovarian cancer cells	
Salvinorine	The Antioxidant Activities of Natural Polysaccharides. Oxidative Stress in Atherosclerosis.	

Table 1: Lists of some non-phenolic and terpenoids

The non-phenolic compounds included into above list, mainly exert some cytotoxic activity which is very beneficial for human body and give very promising result against different types of tumor cells (Perveen & Al-Taweel, 2017).

1.5 Cytotoxicity

Cytotoxicity is basically an abnormal, uncontrolled exposure to other cells or other physical/environmental conditions which mainly occurred by any chemical reaction or stimuli. While showing apoptotic cells growth, necrotic cell death is included into cell lysis and controlled ancestrally. Cell can be toxic or killed in several ways by cytotoxic agents. Basically cytotoxic agents do harm to cell to weaken the cell membrane and cell lysis to stop their (cell) division or further growths (Lynne Eldridge, 2019) (Salih Istifli et al., 2019).

Cancer: Nowadays cancer is second leading reason of death among all the diseases and it has become so challenging because of its powerful interaction with various multiple signaling pathways which involves a variety of target molecules (Farghadani et al., 2016). It is the leading cause of mortality and morbidity as well. Cancer is abnormal, uncontrolled, or irregular unconscious cell growth which may result in tumor, immune system damaging and other fatal disease. Both Fast growing and slow growing cancer cells are there with their action to cellular changes. Numerous types of cancer and their mechanisms vary by their characteristics and can be caused by various reasons. Some reasons like- smoking, alcohol intake, obesity, poor nutrition, genetic, aging, physical inactivity etc. in which some are preventable sometimes and some are not (Nall, 2016). Various types of cancer including,

- Liver cancer
- Leukemia
- Colon cancer
- Thyroid

- Pancreatic
- Bladder
- Melanoma
- Kidney cancer
- Rectal cancer
- Lung cancer
- Breast cancer
- Prostate cancer etc. are very common in recent scenarios (Kandoth et al., 2013).

To prevent cancer, no appropriate treatment is invented yet rather than various approaches.

Some basic approaches are given below:

Chemotherapy: It is a type of cancer treatment in which one or more than one anticancer drug is used. It is one of aggressive form of chemical therapy which is meant to kill cancerous or toxic cell so rapidly in the body. It usually keep preventing the growth or spreading of cancerous cells as those cells are fast growing.

Radiotherapy: Using high doses of radiation to kill the cancerous cell and shrink tumors is one of the advance techniques in cancer treatment. Radiation therapy reduces the size of tumors before killing the remaining cancer cells. X-rays are mostly used in this therapy but other types of energies are used as well.

Hormone therapy: Basically it uses certain medications to balance some hormonal activity. Here main target of those medicines is to deliver throughout the body not only delivered to cancer cell only. It basically acts by adding, removing or blocking the hormones from the body to slow down the cancer cell progression.

Immunotherapy: It aims to boost up immune system to control these cancerous cells. The improved immune system mainly helps the body to fight against infections and some other

disease as well. White blood cells and some organ and tissues from lymph system are creator of immunotherapy. It is known as biological therapy as it uses substances made from living organism to treat cancer.

Stem cell transplant: It is known as bone marrow transplant. Here patients with damaged stem cell got replaced by healthy stem cells. Patient's body needs to be prepared before transplantation by high doses of chemotherapy or radiation therapy. Removing toxic cells is main approach by this type of transplantation.

Surgery: Surgery can be one of the treatments when it comes to spreading of any tumor. Surgery cuts off cancer cell contained in one area. It may removes some of cancerous cell rather than all. In surgery, removing an entire tumor may be harmful for the organ or the body so that debunking is required. Surgery is done to stop the further spreading of those cancerous cells. By doing surgery of a tumor or cancerous cells, it makes other treatment easier and safe.

Various studies show that antioxidants containing food may decrease the rates of cancer risk (Borek, 2004). For example, vitamin e and selenium reduce risk of prostate and colon cancer, on the other hand radiation and anticancer drugs may induce oxidative stress which increases further disease spreading. Carotenoids, may reduce breast cancer risk and ascorbic acid has significant roles in preventing tumor cell growth (Cooperstone & Schwartz, 2016).

1.6 Rationale of the Study

In recent days, there are huge demands for identification of natural plant antioxidants and cytotoxicity for their pharmacological effectiveness. Plant antioxidants mainly prevent the oxidative stress, occurred by reactive oxygen species. There are various methods for identifying biologically and pharmacologically active antioxidant and cytotoxic properties of plant parts. However, literature review revealed that mostly phenolic compounds, flavonoids

etc. possess antioxidant and cytotoxic activity. On but the other hand, non-phenolic compounds and terpenoid are rare in this case of antioxidant and cytotoxic activities. For this reason, this review is an attempt to compile all the non-polyphenolic compounds and terpenoids showing antioxidant and anticancer properties on plant and also their mechanism of actions with some of their benefits.

1.7 Aim of the Study

The aim of this review is to compile all possible non-polyphenolic and terpenoid compounds which have potential in both antioxidant properties and cytotoxicity.

1.8 Objectives

The main objective of this study is given below:

- To get the knowledge on non-polyphenolic and terpenoid containing antioxidant and cytotoxic potential.
- To compile all possible non-polyphenolic and terpenoid compounds having antioxidant and cytotoxic potential.
- To create references for researchers for further investigation.

Chapter 2

Methodology

As the first consideration, this review has done by thoroughly reading a quantity amount of scholarly articles related to the topic and these all are from authentic sources. In addition, these articles were taken from various reliable sources like online database, books, reviewed articles, newspaper according to need. Then, overall information of this review article was taken from those sources and organized in a good manner as it is required. Also, some web pages of some professionals were used as reference here. Some of searching webpages such as PubMed, chem-med, science direct, goggle scholars etc. were used during reviewing this article. Moreover, citation of this review paper was done in Mendely by Elsevier as per required.

Chapter 3

Overview of Some Non Phenolic and Terpenoid Compounds

3.1 Characteristics of Non-phenolic Compound

Pyridinols is a solid which has no color. Again, thiols they are very strong in odor, similar to onion or garlic scent. It has low molecular weight representing that strong smell. They are less soluble in water (Takoi et al., 2009). Limonene it is a liquid which is a colorless and hydrocarbon and known as a terpene. It is found in different plants as well as in some peels of citrus fruits. It has a strong odor similar to orange (Erasto & Viljoen, 2008). Linalool is a non-phenolic compound, a major ingredient of essential oils of various species. This is an odorant which is used to perceive pleasant smell (Aprotosoai et al., 2014). Citral has a strong odor similar to lemon. It is less intense but it is sweeter. It is mobile pale yellow in color (Martins et al., 2017). Phenothiazines is yellow in color and diamond in shape. Slight odor is present and no tastes are there. Lignin: it is a complex polymer. It is insoluble in water and alcohol. It is slightly soluble in alkaline (Birben et al., 2012)

3.2 Mechanism of Action of Non Phenolic and Terpenoid Compound

Some non-phenolic compounds have different mechanism of actions. In first consideration, thiols contain a heap of antioxidants of total body and acts as a very protective against ROS system. Thiols basically transfers oxidative stress to other proteins. However, protein based and molecular level is the main priority of thiol's mechanism of action. It defenses against free radical damages also plays important role in detoxification, apoptosis, signal transduction and other functions as well as involving in various organisms (Ulrich & Jakob, 2019) (Prakash et al., 2009).

Limonene is a powerful antioxidant which plays significant role in preventing cancer. Limonene can block cancer related chemicals or cells. In advanced cancer, tumor contains limonene, which slows down the progression of cancer though it does not guarantee the survival of the host (L., 2011).

Linalool is expert in many ways such as, anxiety and depression, stress, pain, epilepsy, Alzheimer disease, opioid addiction etc. Study shows that it has high antioxidant properties to scavenge free radicals. Also it acts in various compound's synthesis and it can be used as a medicine as it may treat against cancer and several diseases with its antioxidant activities.

The natural non-phenolic compound citral, contain anticancer properties. Antitumor action of citral involves oxidative stress into it. It inhibits some of enzymes and prevents cell proliferations. Citral strengthens antitumor potentiality hence promote the anticancer activity. (Bailly, 2020)

Phenothiazine is used in bipolar disorders and schizophrenia disorders because of their inhibitory characteristics against dopamine receptor. Recent studies show that it exerts a good amount of antitumor effects in which they target various signaling pathways (Wu et al., 2016).

Lignin, a non-phenolic compound found in plant cell walls and it is the most liberal polymer. Numerous uses of lignin include plastic's raw material, petroleum alternative, natural binders, adhesives, resins, agricultural chemicals, textile dyes, vanillin's manufacturing etc. (Amarasekara, 2013). Lignin strengthens and gives rigidity to plants. Moreover, phenolic hydroxyl group in lignin makes it as a strong antioxidant. The antioxidant activities were determined in lignin by the ability of scavenging free radical as it shows clearly in DPPH (a method using diphenyl picryl hydrazyl) (Mahmood et al., 2018).

Comphene, a terpenoid which occur in its enantiometric form and mostly in essential oil including valerian, cypress oil, bergamot oil, camphor oil, etc. Comphene has certain healing characteristics such as anti-inflammatory, antibiotic and anti-cardiovascular diseases, anti-fungal as well. These terpenoids present in significant amount in food, medicine to show these properties. Comphene, p-cymene are strong terpenes which is known as redox active molecule which basically scavenges some reactive species such as hydroxyl radical, nitric oxide and it prevents biomolecule's oxidation. These terpenoids treat against some infectious diseases caused by pain, oxidative stress, inflammation, stress etc. (Quintans-júnior et al., 2013).

Sabinene, a monoterpene, is found in essential oil form of some sub-Sahara African plants. For human health, it is powerful in scavenging free radicals. In addition, it plays role against preventing cancer, heart diseases etc.

The anti-proliferative character of myrcene is found specifically for some cancer cell lines. Hexane and methanol extracts are used to inhibit cell viability and these both extracts reduce motility, migration and invasion of some cell line. Hexane extract decreases nitric oxide production, which shows some anti-inflammatory activity (Bonesi et al., 2018).

Camphor is used very commonly to treat wounds nowadays. First of all, preparing extract using both hot and cold extraction which is assessed its antioxidant properties later. Studies shown that, significant amount of antioxidant effects are found using DPPH method (Muhamad et al., 2019). Camphor is known for so many benefits such as,

- It reduces pain, swelling, inflammation, anxiety, and convulsion,
- Camphor boosts up circulation, digestion, excretion, metabolism and secretion.
- Aromatherapy is mainly depended on camphor oil as its scent gives relieve or refreshment to respiratory system.

- Some common problems like itching, redness, insect bites, acne, rashes are treated well by camphor for its anti-microbial and anti-fungal properties.
- In medicinal terms, it basically shows effects for Anti-depressant, Carminative, Diuretic, sedative, anti-inflammatory, hypertensive, anti-neuralgic, anesthetic etc. in human.
- It induces sleep and treats cold and cough as well (Zuccarini, 2010).

Safrole is a popular essential oil form extracted from natural plant and it exhibits anti-angeogenic, antibiotic activities. Safrole is banned for some of its carcinogenic properties. Though in human, it is not that much huge but it can cause cancer in rodents. Oxidative damage is reason for safrole. Interfering with defense system of neutrophils is also a side effect of safrole (Gad & Pham, 2014).

Estragole, is used as a fragrance and also in flavorings widely. Its smell is close to tarragon as the scent is oily in nature. Essential oil forms are the main source of this terpenoid other sources including basil, dill, tarragon, nutmeg, cinnamon etc. Estragole is widely used in food for flavoring, in some synthesis of some organic compounds in some traditional Chinese medicine. Considering some of common usages of Estragole includes:

- **Reducing fatigue:** Aromatherapy contains Estragole, which is a good medicine to reduce fatigue.
- **Stress relieving:** Estragole is good for relieving stress as tarragon oil helps to serve an effective sleep. Studies shown that, Estragole based oil helps sleep disturbances.
- **Reduce headache:** By applying these essential oils with some other oil like coconut or almond oil can help to reduce headache as they reduce the stress.

- **Good for cognitive function:** it gives positive effects on a person's mind health. For example, it strengthens someone's memory and it also improve someone's way of thinking or mood (Takeda et al., 2017) (Asazawa et al., 2017) (Ponte et al., 2012).

Basically, estragole is an effective source of anti-inflammatory agent and antioxidant which treats various disease caused by oxidative stress (Li et al., 2017).

Methyl Eugenol, which is a phenylpropanoid, is known as Eugenol methyl ether. It is a natural plant compound, acts as flavor or fragrance. Various herbs and fruits contain methyl Eugenol. Such as: tarragon, nutmeg, banana, grapefruit, lemon grass etc. However, methyl Eugenol is known widely for some of its beneficial usages include:

- **Cosmetic preparation:** Methyl Eugenol is used in personal cares and some of cosmetic preparation because of its fragrance. For example, soap, shampoo, perfume etc.
- **Flavoring:** Methyl Eugenol used in flavoring of some food and beverages like ice-cream, candies etc.
- **Anti-microbial effect:** It gives anti-bacterial and anti-fungal activities against some bacterial and fungal organisms.
- **Antioxidant activity:** Methyl Eugenol is a good source of antioxidant and also a very good source of anti-tumor, anti-carcinogenic, cytotoxic properties (Bezerra et al., 2017).

Some health hazards including, eye irritation, nausea, dizziness, skin irritation etc. methyl eugenol is burnable which is hazardous (Data Research Analyst, 2015).

P-cymene, which is a great ingredient for essential oil derived from natural plant. It has antinociceptive effect in rodent. P-cymene has antioxidant properties act in vivo and in brain,

it serves as a neuroprotective agent. Treatment is developing in various diseases by this p-cymene compound (De Oliveira et al., 2015).

Alpha pinene is a terpenoid which acts like a potent antioxidant. It gives anti-inflammatory and anti-carcinogenic properties by inhibiting prostaglandins (Capouet et al., 2004). Alpha pinene has a cooling and soothing effect towards the inflamed tissues. Also, it shows antimicrobial activity in opposition to some dangerous bacteria. Alpha pinene mainly seizes off cancer cell growth which lowers the spreading ability to the other body parts. In addition, it gives some gastro protective effect while consuming at lower exposure. It answers the cell in a promising way. Also it boosts someone's memory by reducing acetylcholinesterase activities and prevent short term memories. On the other hand, large amount of alpha pinene intake is not good for health.

Another terpenoid, D-Borneol, used as a messenger drug in Chinese traditional medicine nowadays in terms of transferring multiple drugs in multiple sites and co-ordinate those drugs effects. It has a BBB opening effect which directly associated with the expression of some genes like *Mdrla* and *Mdrlb*. However, it acts by raising its synergistic effects to maximum level by targeting hypothalamus and hippocampus. However, it increases capacity of the brain dealing out of nanoparticles. Moreover, borneol increases drug efficacy and balance the cell structure and composition at a same time (Gao & Xiaoling Gao, 2019).

Alpha thujene, were found in variety of plants as a terpenoid. It contributes acuteness to the herb's flavor. Alpha thujene binds with GABA receptors as it is a neuro toxic substance. To mention, some properties of alpha thujene are:

- Anti-inflammatory
- Anti-arthritis
- Anti-microbial

- Anti-insecticide (Al-Yasiry & Kiczorowska, 2016)

Another terpenoid, eugenol which is an aromatic compound found in variety of plant like bay leaves, cloves etc. it is used in phenolic dental systems as a topical treatment. In first consideration, anodyne and sedative effects are very common in eugenol. However, it exerts some of very important heart benefits including, antiseptic properties, anti-inflammatory and most importantly exerting anti-oxidant effects. Eugenol hinders sensory nerve system and prostaglandin production. Moreover, it defenses against amyloid peptide, ischemia, excitotoxicity etc. in nervous system. Also treatment in cephalic pain and epilepsy, eugenol is useful (S. H. Park et al., 2011).

In consideration with another terpenoid, alpha terpineol, plays a significant role in human's life and industries field as well. Some of important biological applications are in range of alpha terpineol. For example, it shows a quality amount of anticancer properties as an antioxidant. Another applications like, anti-hypertensive, anti-convulsant, anti-ulcer, anti-nociceptive etc. Effects are exerted by alpha terpineol. In addition, giving skin penetration to insecticidal protection are included here. Also in cosmetic preparation, alpha terpineol has a great implementation by promising as a good candidate in pharmaceutical industries and people's day to day life (Khaleel et al., 2018).

Terpinene-4-ol is a very good terpenoid in terms of anti-tumor properties by showing impressing results in preventing numerous cancer models. It basically exerts its anti-tumor effects by activating caspase-dependent apoptosis which is in melanoma cells. In addition, terpinene-4-ol has some other biological activities such as anti-proliferative and anti-inflammatory (Lin et al., 2012).

Phellandrene, is another terpenoid having powerful antifungal activities in which they increase the cell permeability and hampers the cell integrity. Phellandrene metabolizes in two

possible pathways. One of the ways requires redox reaction to produce phellanduric acid and phellandric acid. Another way is in conjugation phase and hydroxylation (Zhang et al., 2017)

δ -3-carene, a terpenoid known for its great allergenic properties. Studies shown that it is found as a microbolite in-vitro by using human lung microsomes and liver (Tisserand & Young, 2014).

Chapter 4

Discussion

The main objective of this paper was to compiling some non-phenolic compounds and some terpenoids present in plants. These compounds have quality amounts of antioxidant properties along with some other health benefits such as anti-inflammatory, anti-microbial, anti-tumor, anti-allergenic, antiseptic etc. properties. Anti-inflammatory and anti-microbial characteristics were mostly common among all the non-phenolic compounds and terpenoids. Anti-diabetic property is also a great thing to focus on. Mainly, anticancer and antioxidant properties findings are the main goal lying into this review paper. Some compounds play very significant role in preventing cancer and further cell growth as well as in tumor cell spreading. Cancer generations by various reasons are described nicely in this paper with all the cancer types. Some of cancer treatments like, chemotherapy, radiotherapy is most common treatment for cancer and also some antioxidants derived from dietary foods are commonly used for cancer prevention and other diseases prevention as well. However, the diseases caused by free radical generation, are treated well with these antioxidants. These antioxidants basically scavenge the free radicals by various possible ways including breaking free radical chain reaction, decreasing oxygen concentration etc. also it varies reaction to reaction to serve the same scavenging activity. To explain, free radicals generate some damages in human body by oxidative stress in reactive oxygen system. ROS affects the other cell generation or expression by balancing redox-sensitive transcription factors. By changing the original cell structure, it mutates tumor and disrupt some disease which are called as free radical disease. From the table, it's seen all the compounds with their structure and some of their tests done so far. Moreover, the details of those compounds with their basic mechanism of action and effects on human body will influence the health sectors by introducing new drugs and remedies. In addition, the pharmacological studies or previously done studies on

those antioxidants listed in the table, influences further experiments and the studies related to cancer prevention. Thus, it is an understandable evident that there are so many plants having non-phenolic compounds and terpenoids but their established uses are yet to be approved scientifically. These compounds having antioxidant and anticancer properties may help in near future for discovering new lead compound in drug having many more therapeutic efficacies.

Chapter 5

Conclusion and Future Direction

In conclusion, both non-polyphenolic compounds and terpenoid in plants show some valuable effects like preventing cancer, anti-microbial activity, anti-fungal activity etc. The review is about compilation of almost all non-polyphenolic and terpenoid compounds which contribute into cytotoxicity and antioxidant properties. Various studies have showed that nonpolyphenolic and terpenoids can also have antioxidant and cytotoxic properties. That is why this review is focused on compiling non-polyphenolic and terpenoid compounds in plants with antioxidant and cytotoxic activity. However, non-phenolic compounds and terpenoids in plants are a great source of antioxidant and anticancer properties.

This review has been written with a view to facilitate the work of future researchers who wants to conduct lab based work with these compounds. It will help them to understand if these compounds are already been investigated or not by other scientists. Moreover, it will serve as a future documentation for other researchers.

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