



The Anticancer Properties Of Flavonoids In Lung Cancer: A Review Of The Current State Of Knowledge

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ABSTRACT

Flavonoids, a class of naturally occurring polyphenolic compounds, have shown significant potential in cancer prevention and treatment, particularly for lung cancer. Widely present in fruits, vegetables, and plant-derived foods, flavonoids exhibit a range of biological properties, including antioxidant, anti-inflammatory, and anticancer effects. Studies suggest that dietary flavonoids can serve as effective agents to mitigate lung cancer risk by targeting various carcinogenic pathways. The anticancer mechanisms of flavonoids involve multiple molecular pathways. They exhibit antioxidative effects by scavenging free radicals and preventing DNA damage, which can lead to mutations and tumor initiation. Furthermore, flavonoids modulate key signaling pathways such as PI3K/Akt and MAPK, inhibit cell cycle progression, and induce apoptosis in cancer cells. Notably, flavonoids target receptor tyrosine kinases (RTKs), such as EGFR and VEGFR, which play critical roles in lung cancer development. By inhibiting these receptors, flavonoids disrupt signaling cascades that promote tumor proliferation and survival. In conclusion, flavonoids offer a natural, safe, and cost-effective approach to lung cancer prevention and treatment.

KEYWORDS: Flavonoids, Receptor tyrosine kinase, Lung cancer.

1.INTRODUCTON

Essential therapeutic components are constantly available from plants. Since ancient times, they have been a source of medicines to treat a variety of conditions. Complex chemical substances called polyphenols can be found in many plant-based diets. The fundamental building block of polyphenols is the phenolic ring, which is frequently divided into phenolic acids and phenolic alcohols. The two main types of polyphenols are flavonoids and non-flavonoids, which collectively comprise over 8000 distinct compounds.^[1]

Examples of non-flavonoids include lignans, stilbenes, phenolic acids, nonphenolic metabolites, and other polyphenols. A series of genetic and epigenetic changes brought on by long-term exposure to carcinogens such as smoking, radon in homes, burning fossil fuels, exhaust fumes from moving cars, and inhaling pesticides combine to cause lung cancer.^[2] Natural substances originating from plants, known as phytochemicals, have been utilized to treat a number of illnesses, including cancer. Studies both in vivo and in vitro have shown their impact on the growth, metastasis, and proliferation of tumours. Natural compounds also continue to be used because they are more affordable, readily available, and have a higher tolerance than synthesized molecules. Natural sources provide around 8,000 distinct polyphenolic chemicals, including phenolic acids, flavonoids, stilbenes, and lignans (fruits, vegetables, and seeds) Flavonoids are phytochemicals that are members of the polyphenol class, which has more than 4000 members.^[3]

The health benefits of naturally occurring flavonoids which are further classified as flavones, flavanols, flavanones, flavanols, anthocyanins, and isoflavones have received a lot of attention lately. Since flavonoids have comparable functional structures, the substituent groups the chemical structure shown in the figure are typically responsible for the functional variation. Flavonoids are thought to provide molecular template for the development of innovative therapeutic medicines for a variety of diseases, including lung cancer, and have numerous positive impacts on human health. Initially, the primary biological action of flavonoids was thought to be their ability to prevent the generation of reactive oxygen species (ROS), which affected various molecular mechanisms changed in tumor cells and included a wide variety of important cellular processes.^[4]

2. CLASSIFICATION OF FLAVONOIDS

The carbon of the C ring, to which the B ring is linked, as well as the degree of unsaturation and oxidation of the C ring, determine which subgroups of flavonoids are formed. Isoflavones are flavonoids in which the B ring is bonded to the C ring at position 3. Neoflavonoids are those in which the B ring is joined in position 4, whereas those in which the B ring is linked in position 2 can be further separated into multiple subgroups according to the structural characteristics of the C ring.^[5]

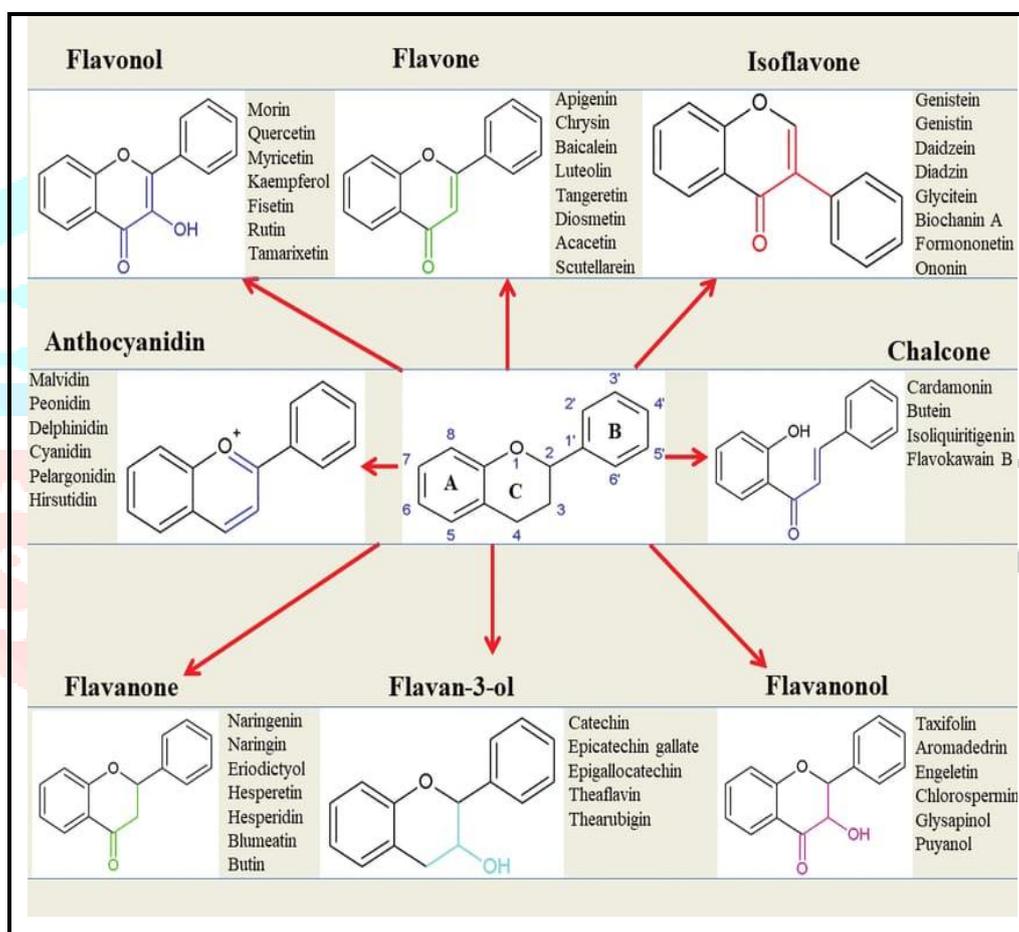


Figure 1: classification and structures of most prevalent flavonoids^[6]

3. EFFECTS OF FLAVONOID ON CANCER-RELATED BIOLOGICAL PATHWAYS

A variety of pathways, such as antioxidant, anti-inflammatory, and anti-proliferative properties, as well as the inhibition of bioactivating enzymes and the stimulation of detoxification enzymes, have been linked to the anti-neoplastic actions of flavonoids.^[7]

Furthermore, flavonoids induce apoptosis in cancer cells by downregulating-apoptotic proteins like Bcl-2 and activating pro-apoptotic proteins like caspases and Bax. By focusing on vascular endothelial growth factor (VEGF) pathways, they also prevent angiogenesis and reduce the blood flow to tumours. Furthermore, flavonoids inhibit metastasis by increasing cell adhesion and decreasing matrix metalloproteinase (MMP) activity.^[8]

4. RECEPTOR TYROSINE KINASES IN LUNG CANCER

A class of transmembrane proteins known as receptor tyrosine kinases has an extracellular ligand-binding area as well as a cytoplasmic region that is composed of three sites: the carboxy (C)-terminal, the juxta membrane regulatory region, and the tyrosine kinase domain. They carry out the function of cellular messengers, carrying information from the outside to the inside of the cell and producing a variety of effects. They play important roles in a variety of cellular processes, such as metabolism, apoptosis, cell cycle regulation, proliferation, and others that affect how cells behave.

Four basic steps make up the mechanism of RTK activation:[30]

- a. Ligand binding to RTK
- b. Receptor dimerization
- c. Trans-phosphorylation of tyrosine residues in the TKD activation loop, disrupting auto inhibitory interactions
- d. Newly formed phosphotyrosines act as sites for the recruitment of cytoplasmic.

signaling molecules that contain the src-homology-2(SH2) and phosphotyrosine binding (PTB) domain. As a result, a ligand that binds to the following proteins: PDGFR, Vascular Endothelial Growth Factor Receptor, Insulin Receptor, Insulin Like Growth Factor 1 Receptor, FGFR, and Epidermal Growth Factor Receptor (EGFR, InsR, and IGF1R, respectively); After binding to RTKs, molecules containing SH2/PTB are eventually recruited directly or indirectly through other proteins that are docked to RTKs. This then triggers signaling pathways including JAK/STAT, PI3K, and MAPK, which result in either death or cell growth. Lung cancer alters most of the RTKs. This section will concentrate on a few RTKs, such as EGFR, VEGFR, PDGFR, FGFR, IGF1R, and c-Met, that are typically changed in lung cancer. Gain-of-function mutations, overexpression, chromosomal rearrangements, and autocrine activation are among the many RTK changes seen in cancer. EGFR is the most researched RTK in lung cancer mutations, overexpression.

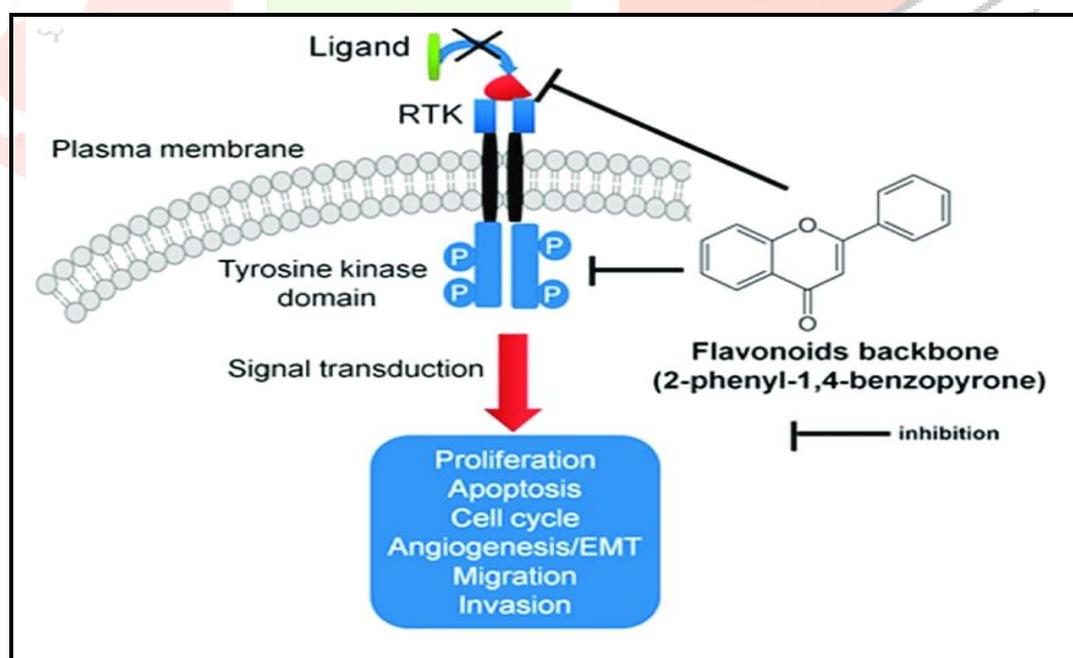


Figure 2: mechanism of action of flavonoids as rtk inhibitor^[9]

5. ROLE OF LUTEOLIN IN LUNG CANCER

One of the most highly esteemed naturally occurring plant-derived substances is the flavonoid luteolin (3',4',5,7-tetrahydroxyflavone), which is widely distributed in a variety of herbaceous and vegetable plants. In addition to fruits, vegetables, and herbs, luteolin is also found in foods including dried parsley, Chinese celery, and radicchio. Lutein is a significant representative flavonoid that has two benzene rings and a

heterocyclic ring containing oxygen. The hydroxyl groups located at carbon atoms 5, 7, 3', and 4', along with the double bonds between them, are essential for the pharmacological properties of luteolin, which include anti-inflammatory, anti-tumor, antioxidant, and neuroprotective activities.

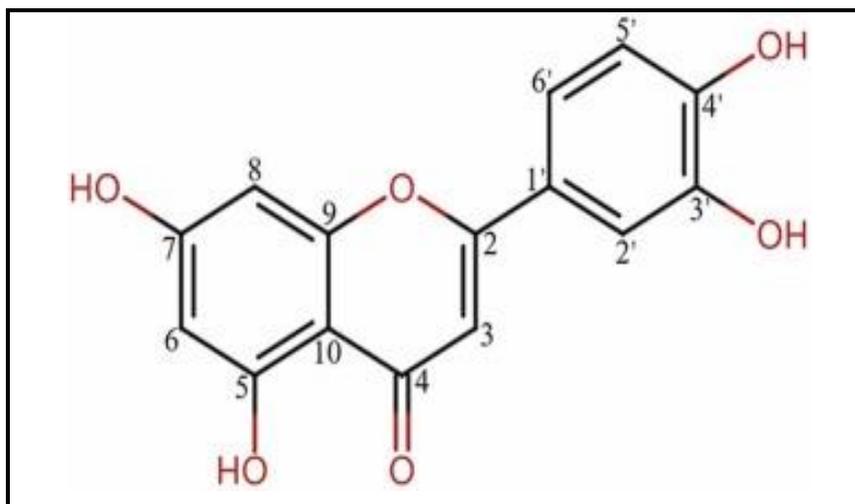


figure no 3: structure of Luteolin ^[10]

6. MECHANISM OF LUTEOLIN

6.1 Pro-apoptotic effect:

Apoptosis is a type of planned cell death that is genetically encoded. Apoptosis is widely distributed in humans and is essential to healthy bodily growth and equilibrium. The mitochondrial, endoplasmic reticulum (ER), and death receptor pathways are the three main molecular mechanisms that underlie apoptosis brought on by DNA damage brought on by external stimuli. The molecules that make up luteolin are interconnected and interact with one another. Members of the tumor necrosis factor (TNF) family, FAS and TRAILR-related apoptosis-inducing ligand receptor (TRAILR) have the ability to cause tumor cells to undergo apoptosis. ^[11]

6.2 Inhibition of Cell Proliferation:

Tumor cells are biologically unique in that they have the capacity to continuously proliferate and provide themselves with adequate growth signals. One of the main causes of the difficulty in totally eliminating tumor cells is malignant growth. Changing the distribution of the cell cycle and causing cell cycle inhibition are regarded as successful anti-cancer strategies. ^[12]

In tumor cells, the mitotic cycle can be divided into four stages: pre-DNA synthesis (G1 phase), late DNA synthesis (G2 phase), mitosis (M phase), and DNA synthesis (S phase). The cyclin-CDK complex, which is produced by the binding of cyclin and cyclin-dependent kinase (CDK), is at the center of the precise and tight regulation of different regulator levels, which is necessary for the progression of the cell cycle. ^[13]

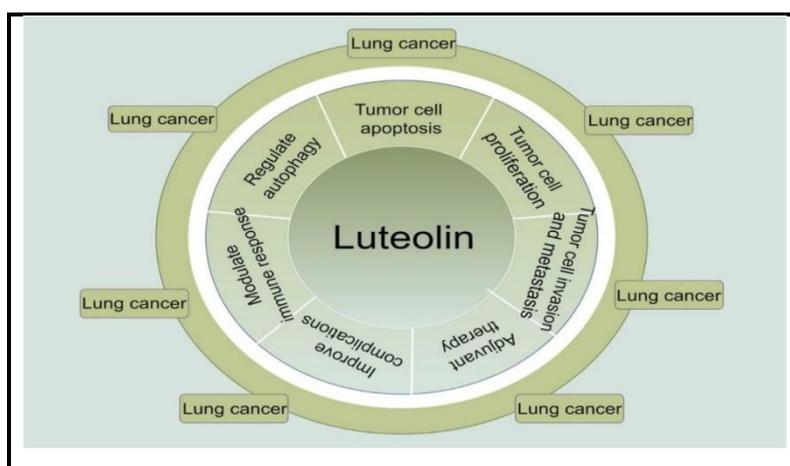


Figure 4: action of luteolin ^[14]

7.CONCLUSION

Flavonoids offer a natural and promising approach to lung cancer therapy through their ability to target multiple oncogenic pathways. Their antioxidant, antiproliferative, and anti-inflammatory properties, coupled with their role in apoptosis and angiogenesis regulation, make them valuable in complementing existing cancer treatments. Future research should focus on clinical trials and developing flavonoid-based drugs to optimize their therapeutic potential. By integrating these compounds into comprehensive treatment plans, we can pave the way for more effective and less toxic cancer therapies.

8.REFERENCES

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