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# A comprehensive and current review on the role of flavonoids in lung cancer–Experimental and theoretical approaches

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## ARTICLE INFO

## ABSTRACT

*Background:* It is well-known that flavonoids, which can be easily obtained from many fruits and vegetables are widely preferred in the treatment of some important diseases. Some researchers noted that these chemical compounds exhibit high inhibition effect against various cancer types. Many experimental studies proving this ability of the flavonoids with high antioxidant activity are available in the literature.

*Purpose:* The main aim of this review is to summarize comprehensively anticancer properties of flavonoids against the lung cancer in the light of experimental studies and well-known theory and electronic structure principles. In this review article, more detailed and current information about the using of flavonoids in the treatment of lung cancer is presented considering theoretical and experimental approaches.

*Study Design:* In addition to experimental studies including the anticancer effects of flavonoids, we emphasized the requirement of the well-known electronic structure principle in the development of anticancer drugs. For this aim, Conceptual Density Functional Theory should be considered as a powerful tool. Searching the databases including ScienceDirect, PubMed and Web of Science, the suitable reference papers for this project were selected.

*Methods:* Theoretical tools like DFT and Molecular Docking provides important clues about anticancer behavior and drug properties of molecular systems. Conceptual Density Functional Theory and CDFT based electronic structure principles and rules like Hard and Soft Acid-Base Principle (HSAB), Maximum Hardness Principle, Minimum Polarizability, Minimum Electrophilicity Principles and Maximum Composite Hardness Rule introduced by one of the authors of this review are so useful to predict the mechanisms and powers of chemical systems. Especially, it cannot be ignored the success of HSAB Principle in the explanations and highlighting of biochemical interactions.

*Results:* Both theoretical analysis and experimental studies confirmed that flavonoids have higher inhibition effect against lung cancer. In addition to many superior properties like anticancer activity, antimicrobial activity, antioxidant activity, antidiabetic effect of flavonoids, their toxicities are also explained with the help of published popular papers. Action modes of the mentioned compounds are given in detail.

*Conclusion:* The review includes detailed information about the mentioned electronic structure principles and rules and their applications in the cancer research. In addition, the epidemiology and types of lung cancer anticancer activity of flavonoids in lung cancer are explained in details.

## Introduction

In the last decade, natural sources gained interest due to their numerous therapeutical activities. Scientific studies led the isolation of active metabolites from natural sources with improved bioactivities. Moreover, chemical diversity of natural products guided the production of new and more effective medications namely development of novel treatment regimens (Cragg et al., 2009; Lautié et al., 2020; Rodriguez-Canales et al., 2016b). The desire for safer drugs with less environmental and mammalian toxicity is a major concern in this purpose. Natural products offer potent anti-cancer properties with lower adverse effects when compared with the conventional chemotherapeutic agents due to chemoresistance as well as high cytotoxicity. Both paclitaxel and vincristine are invaluable representatives of natural products with anticancer activity. Recently, utilization of natural products in clinical therapy is increased due to their being easily accessible, cost-effective, and more efficient during treatment (Buyel, 2018; Dutta et al., 2019; Kanarek et al., 2020; Liu et al., 2020a; Shoji and Yuan, 2021). Remarkable chemical structures and pleiotropic activities of most secondary metabolite groups (alkaloids, terpenoids, flavonoids, quinones, and steroids) are investigated regarding their potential anti-cancer activities or their being scaffold for potent anti-cancer medicines (Nwodo et al., 2016; Pourakbari et al., 2020) . Amongst, flavonoids are one of the important and widespread classes of secondary metabolites, found in most fruits, vegetables, and certain beverages. Flavonoids are mostly synthesized in particular organs of the plants to aid their growth and protection from pathogens, to color and give the aroma, and to attract pollinators (Dias and Pinto, 2021) . Flavonoids also have a role in protection of plants from various biotic and abiotic stress, and act as unique UV filters (Takahashi and Ohnishi, 2004). Their remarkable antioxidant and anti-inflammatory activities made flavonoids one of the indispensable compounds in a variety of nutraceutical, pharmaceutical, medicinal, and cosmetic products. In addition, flavonoids are very attractive compounds due to their anti-mutagenic, anti-carcinogenic and enzyme inhibitory properties (Castañeda-Ovando et al., 2009; Falcone Ferreyra et al., 2012; Walker et al., 2000). Especially, the anticancer activity and activity mechanisms of flavonoids are identified by many different *in vitro* and *in vivo* models (Fraga et al., 2019; Hasima and Ozpolat, 2014; Jucá et al., 2020; Pang et al., 2021)

Due to the importance of flavonoids as a therapeutical lead, it was aimed to review the trends of research and development on flavonoids, their applications as the treatment of lung cancer and health benefits along with broad classification and future research directions.

### Search results and study characteristics

According to the PRISMA criteria, we designed the review. Initially, 17,098 records were obtained from the well-known databases (13,613 from ScienceDirect, 2027 from PubMed, and 1458 from Web of Science). The search results were then limited to research articles, review articles, brief communications, and systematic and mini reviews. As a result, 11,554 articles were subject to title and abstract screening. 3565 records were eliminated After duplication check (512) ,7477 articles were finally included in the qualitative analysis for the first part of this study.

The pool of included studies was then classified according to (a) flavonoid class, (b) flavonoid name, (c) disease (lung cancer), (d) *in vitro* testing, and (e) *in vivo* testing. The characteristics of the included studies are summarized in Tables 1 and 2. A total of 508 research and review articles were considered. All included articles reported lung cancer related to *in vitro* and/or *in vivo* experiments for different classes of flavonoids.

### Classification of flavonoids

Flavonoids are group of secondary metabolites with variable phenolic nature. Basic flavonoid skeleton is composed of fifteen-carbon skeleton with two benzene rings and a heterocyclic pyrane ring. There are diverse subgroups such as flavones, flavanones, flavanols, flavones, neoflavonoids, catechins, anthocyanins and chalcones etc. according to the degree of unsaturation, oxidation, and substitution on those rings (Fig. 1) (Panche et al., 2015).

### Biological effects of flavonoids

It is well-known that flavonoids are among the widely studied classes of diphenylpropanes. These compounds include two aromatic rings bonded through three carbons in their molecular structure. In a recent paper, Qiu et al. (2018) presented a detailed study explaining the mechanism and action mode of the subclasses of flavonoids (Qiu et al., 2018). The authors noted that flavones and isoflavones are closely linked to multi-cancer related pathways. Flavan-3-ols are more effective on cellular processing and lymphocyte regulation while flavones are effective on the cardiovascular diseases. Isoflavones is significantly connected to the cell multisystem disorders. The results obtained showed that there is a strong linkage between chemical structures, side chains of the compounds and their biological activities.

Some researchers showed that flavonoids exhibit antibacterial activity via three mechanisms.

- Damaging the cytoplasmic membrane by perforation mechanism (Plaper et al., 2003) and decreasing the membrane fluidity (Wu et al., 2003)
- Via inhibition effect on energy metabolism (Avila et al., 2008)
- Inhibiting the synthesis of nucleic acids (Mirzoeva et al., 1997). Action modes regarding to the anticancer and antibacterial behaviors of flavonoids are visually summarized in Fig. 2 and 3. The mentioned figures were taken from the paper penned by Kaleem et al. (Kaleem et al., 2015).

Secondary metabolites often distributed among limited taxonomic groups in plant kingdom (Croteau et al., 2000). There has been increased interest on flavonoids since they have a number of protective and therapeutic functions in human body. Due to the imprtance of natural compounds, especially flavonoids, plant cell tissue culture is preferred to create the similar quality chemical compounds as the parent (Anand, 2010). Plant tissue culture technologies for flavonoid production have advanced well beyond expectations (Hussain et al., 2012). Plant tissue culture is an aseptic technology that allows for the production of desired quality and quantity of plants and metabolites by manipulating nutrients, culture conditions, and phyto-hormone supply. It is feasible to get synthesis of the required chemicals at levels equivalent to those natural metabolites using plant cell culture.

Flavonoids have a wide range of health beneficial effects such as antioxidant (Srivastava et al., 2015a), anti-inflammatory (Ferraz et al., 2020), anti-mutagenic (Snijman et al., 2007) and anti-carcinogenic (LeJeune et al., 2015) , and modulatory activity on key cellular enzyme functions (Kim et al., 2004). Several research have been conducted in recent years on the ability of flavonoids to serve as antioxidants, and key structure–activity correlations of antioxidant activity have been identified (Ren et al., 2003) (Srivastava and Bezwada, 2015). Ren et al. (2003) revealed that flavonoids showed their protective role in carcinogenesis via inhibiting various cytochrome P450 isozymes, which are responsible for the formation of a number of procarcinogens. Furthermore, many flavonoids show their antimicrobial and insecticidal activities via interacting with nucleic acid and proteins. Hence, flavonoids might be considered as medicine and agricultural tool as pesticides (Wink, 2004). In addition, it was explained that flavonoids aid in synthesis of metabolizing enzymes such as glutathione-S-transferase, quinone reductase and uridine 5-diphospho-glucuronyl transferase that enhance the elimination of carcinogens from the body (Moon et al., 2006).

With respect to numerous bioactivities of flavonoids, their

**Table 1**

*In vitro* studies of anti-cancer effects of flavonoids in the treatment of lung cancer.

| Phycochemical class | Phytochemicals | Biological system | Approach | Biological effect | Molecular target | Reference |
|---|---|---|---|---|---|---|
| **Flavones** | Lutein | NCI-H460 and HEK-293T cell lines | Apoptosis assay, western blotting, RT-qPCR | Apoptosis activation | Bad↑, Bcl-2↓, Bax↑, caspase-3↑, and Sirt1↓ | (Ma et al., 2015) |
| | | H1299 and H460 cells lines | Immunoblot analysis, PI assay | Apoptosis activation | p38/ROS/caspase cascade↑ | (Cho et al., 2015) |
| | | A549 cells | MTT assay, migration and invasion assays, western blot | induce apoptosis through regulating the phosphoinositide 3-kinase (PI3K)/AKT signaling molecules | Bcl-XL↓, Bcl-2↓, Bax↑, | (Zhang et al., 2018b) |
| **Flavones** | Luteolin | A549 cells | MTT assay, migration and invasion assays | viability, adhesion to fibronectin, invasion, and migration | | (Naso et al., 2021) |
| | | H358, H460, H2122, and A549 | MTT assay, colony assay, RT-qPCR, western blot, IL-2 assays | Anti-proliferation, Apoptosis activation, MUC1-C/STAT3 signaling | MUC1-C and PD-L1↓, inhibition of IFN-γ-induced PD-L1 expression | (Jiang et al., 2021) |
| **Flavones** | Apigenin | A549 cells | MTT assay, colony assay, Transwell assay, western blot | Anti-proliferation, anti-migration, and anti-invasion effects | ↓Akt affecting PI3K signaling | (Zhou et al., 2017) |
| | | H1299 | Apoptosis assay, western blotting, RT-qPCR | Apoptosis activation, glucose metabolism | ↓ GLUT1 | (Lee et al., 2016) |
| | | H358, H460, H2122, and A549 | MTT assay, colony assay, RT-qPCR, western blot, IL-2 assays | Anti-proliferation, Apoptosis activation, MUC1-C/STAT3 signaling | MUC1-C and PD-L1↓, inhibition of IFN-γ-induced PD-L1 expression | (Jiang et al., 2021) |
| | | A549 and H1299 | Cell proliferation assay, Apoptosis assay, western blotting, RT-qPCR | induce apoptosis through regulating the NF-κB, PI3K/AKT and JNK signaling pathway | Bad↑, Bax↑, Bcl-2↓, Bcl-XL↓, DR4 and DR5↑ NF-κB transcriptional activity↓, PI3K/AKT cascade↓ and activation of JNK-c-JUN pathway↓ | (Chen et al., 2016) |
| | | A549, H1975, and HCC827 NSCLC cell lines | Transwell migration and invasion assays, RT-qPCR | Inhibition of the migration/invasion of NSCLC cells | Akt and Snail/Slug↑ | (Chang et al., 2018b) |
| | | A549 cells | MTT assay, migration and invasion assays | viability, adhesion to fibronectin, invasion, and migration | | (Naso et al., 2021) |
| **Flavones** | Baicalein | A549 and H1299 cell lines | Western blot, RT-qPCR | Inhibition of cell proliferation, cell invasion and EMT, down-regulation of Notch1 and hes-1 expression | Cyclin D1 and CDK1↓ | (Su et al., 2018) |
| | | A549 cells | MTT assay, migration and invasion assays | viability, adhesion to fibronectin, invasion, and migration | | (Naso et al., 2021) |
| | | A549 cells | MTT assay, Transwell migration, RT-qPCR | Anti-proliferation, anti-migration/invasion effects, inhibiting the RhoA/ROCK signaling pathway | ↓RhoA, ROCK1 and ROCK2 | (Zhang et al., 2020c) |
| | | H1299 and A549 cell lines | Transfection, immunoprecipitation assays, western blot analysis, Confocal microscopy, Autophagy assays | Inhibition of MAP4K3 kinase activity | MAP4K3↓ | (Li et al., 2021a) |
| | | A549 cells | MTT assay | Cytotoxic effect | | (Marzec et al., 2020) |
| | | H1299 and A549 cell lines | MTT assay, migration and invasion assays, western blot analysis | preventing NSCLC invasion and metastasis | | (Zhang et al., 2020a) |
| | | A549 and H460 cells | | Increase cisplatin sensitivity and inhibit proliferation | miR-424–3p | (Lu et al., 2018) |
| **Flavones** | Chrysin | A549 cells | MTT assay | Cytotoxic effect | | (Marzec et al., 2020) |
| **Flavones** | Nobiletin | H1299 cells | | Inhibit cell migration and invasion | miR-200b | (Gao et al., 2015) |
| **Flavonols** | Quercertin | JB6 Cl41 and A549 cell lines | Anchorage independent transformation assay, Microscale thermophoresis | Suppression of cells proliferation | Aurora B kinase↓ | (Zhu et al., 2016) |
| | | NCI-H358 and A549 cell lines | Apoptosis, microarray | Antiproliferative effects | Caspase-3↑ | (Cincin et al., 2014) |
| | | A549 cells | RT-qPCR | Decrease of tight junction mechanisms | miR-16↑ | (Sonoki et al., 2015) |

Table 1 (*continued*)

| Phycochemical class | Phytochemicals | Biological system | Approach | Biological effect | Molecular target | Reference |
|---|---|---|---|---|---|---|
| **Flavonols** | Kaempferol | A549 cell line | MTT assay, Transfection, PCR | Inhibition of cell proliferation | STAT3↓, claudin-2↓ | (Sonoki et al., 2017) |
| | | A549 cells | Apoptosis assay, RT-qPCR, western blotting | Cell apoptosis, inhibition of proliferation | miR-340↑ | (Han et al., 2018) |
| **Flavonols** | Fisetin | A549 cell line | MTT assay, RT-qPCR, flow-cytometry | Apoptosis activation | ERK1/2↓ | (Wang and Huang, 2018) |
| **Flavonols** | Myricetin | A549 cell line | MTT assay, Apoptosis assay, RT-qPCR | Inhibition of cell proliferation and cell cycle progression, inducing apoptosis, | EGFR↓, P53↑ | (Rajendran et al., 2021) |
| | | A549 and H1299 | Cell proliferation assay, colony forming assay, Apoptosis assay, western blotting | Inhibition of cell, proliferation, inducing apoptosis, | caspase-3↑, | (Zhang et al., 2014) |
| **Flavanone** | Hesperetin | A549 cell line | RT-PCR, western blot | Inhibition of cell proliferation | ERK1/2↓, HFKb-p65↓ | (Ramteke and Yadav, 2019) |
| | | A549 cell line | | Inhibition of cell proliferation and cell cycle progression | | (Xia et al., 2018) |
| | | A549 and NCI-H358 cell lines | Cell proliferation, cell cycle, apoptosis assay | Anti-proliferative and apoptotic effects | | (Cincin et al., 2015) |
| | | A549 and A549/DDP cells | Cell proliferation, Apoptosis assay, RT-qPCR, western blotting | Inhibition of cell proliferation, Apoptosis activation | P-gp↓, p65↓ | (Kong et al., 2020) |
| **Flavanone** | Naringenin | A549 cell line | RT-PCR, western blot | Suppression of Akt activity and the downregulation of MMP-2 and −9 | Akt↓ | (Chang et al., 2017) |
| | | A549 cell line | Apoptosis assay, western blot | Cells apoptosis | Bid and DR5↑ | (Jin et al., 2011) |
| | | A549 cells | Cell proliferation assay, wound-healing assay, migration assay, western blotting, RT-qPCR | Cytotoxic effect Inhibit cell migration and invasion | caspase-3↑, MMP-2 and MMP-9↓. | (Shi et al., 2021) |
| **Flavanone** | Naringin | H69AR | | Suppress cell growth and induce apoptosis | miR126 | (Chen et al., 2018) |
| **Flavanone** | Eriodictyol | A549 cell line | Cell proliferation, cell cycle, apoptosis assay, western blot | Inhibition of cell proliferation and cell cycle progression, inducing apoptosis, mTOR/PI3K/Akt activation | PI3K/AKT/m-TOR↓, Bcl-2↓, Bax↑ | (Zhang et al., 2020b) |
| **Flavanone** | Scutellarin | A549 cell line | Cell proliferation, cell cycle, colony forming assay, apoptosis assay, western blot | Inhibition of cell proliferation and cell cycle progression, inducing apoptosis, inhibition of AKT/ mTOR/4EBP1 and STAT3 | ↑BAX/BCL-2 ratio and cleaved (active) caspase-3, ↑ AKT/mTOR /4EBP1 and STAT3 pathways. | (Cao et al., 2019) |
| | | A549 and H1975 | Cell proliferation, apoptosis assay, western blot | Inhibition of cell proliferation inducing apoptosis, inhibition of AKT/mTOR | ↓AKT/mTOR pathway, ↑Bcl2/Bax | (He et al., 2021) |
| **Flavanols** | EGCG | H1299 cell line | Cell proliferation, apoptosis assay, western blot | Suppressing proliferation, inducing apoptosis | PI3K/Akt↓ | (Gu et al., 2018) |
| | | A549 cell line | Cell culture and transfection, Western blot, Flow cytometry | Decreased EGF-induced EGFR, Akt and ERK1/2 activation. | EGFR↓ | (Ma et al., 2014) |
| | | A549 and NCI-H1299 cell lines | Scattering assay, wound healing assay, *in vitro* invasion assay, qRT-PCR, Western blot, confocal microscopy | Cell proliferation, EMT | TGFβ↓, Smad2↓ and Erk1/2↓ | (Liu et al., 2012) |
| | | A549 cell line | HAT activity assays, Immunoprecipitation and western blot analysis, RT-PCR | TGF-β1-induced EMT inhibition | TGFβ↓, Smad2↓, Smad3↓ | (Ko et al., 2013) |
| | | A549 cells | Microarray, RT-qPCR | Reduction of cell growth, hypoxia | miR-210↑ | (Wang et al., 2011) |
| | | A549 cells | NGS | Inhibition of proliferation and migration | miR-212↓ miR-155↑ | (Bhardwaj and Mandal, 2019) |
| | | A549 cells | | Induce apoptosis | hsa-miR-125a-3p | (Zhou et al., 2014) |
| **Isoflavones** | Daidzein | NSCLC cells | TUNEL assay. Real-time PCR and western blotting | Inducing apoptosis | STK3, STK4↓, YAP1↓, caspase3↓ | (Chen et al., 2017) |

**Table 1** (*continued*)

| Phycochemical class | Phytochemicals | Biological system | Approach | Biological effect | Molecular target | Reference |
|---|---|---|---|---|---|---|
| **Isoflavones** | Genistein | H446 cell line | Apoptosis assay, colony assay, RT-PCR, western blot | Apoptosis and G2/M phase cell cycle arrest | Cdc25B↓, cyclin B1↓, survivin↓ | (Tian et al., 2014) |
| | | A549 cell line | Apoptosis assay, qRT-PCR, Western blot | Inhibition of cell proliferation, induce cells apoptosis | Bax↑, Bcl-2↓ | (Zhang et al., 2018a) |
| | | A549 cells | Apoptosis assay, western blotting | Apoptosis and promotes caspase-3/9 activation | miR-27a↓ | (Yang et al., 2015) |
| **Anthocyanidins** | Delphinidin | A549 cell line | Cell viability assay, Western blot, RT-PCR, Matrigel plug assay | Suppression of the ERK, mTOR, and p70S6K pathways | HIF-1α↓ VEGF↓ | (Kim et al., 2017) |
| | | NCI-H441, SK-MES-1 and A549 cell lines | Western blot, Cell viability assay | Apoptosis and angiogenesis | ↑caspase-3/9, ↓ anti-apoptotic proteins (Bcl2, Bcl-xL and Mcl-1), ↑pro-apoptotic proteins (Bax and Bak);↓EGFR and VEGFR2 | (Pal et al., 2013) |

antioxidant activity comes into prominence (Han Jie et al., 2020; Hertog et al., 1997; Ishikawa et al., 1997; Mannino et al., 2021; Song et al., 2021). Oxidative stress is an inevitable consequence of aerobic life, and it is clearly related to the etiology of a wide range of chronic and acute diseases such as cancer, diabetes, cardiovascular disorders, and the aging process, etc. The detrimental effect of reactive oxygen species (ROS) causing potential biological damage is termed oxidative stress. This occurs in biological systems when there is an overproduction of ROS on one side and a deficiency of enzymatic and non-enzymatic defense systems on the other. Briefly, oxidative stress arises from the metabolic reactions that use oxygen and represents a disturbance in the balance of oxidant/antioxidant reactions in living organisms. Antioxidants inhibit radical-producing mechanisms and increase the activity of endogenous antioxidants, protecting cells from free radical damage (Srivastava and Bezwada, 2015).

The best expressed property of flavonoids is the ability to trap free radicals. Moreover, they are known to have the optimal chemical properties because they act both as hydrogen and electron donors and have the ability of chelating metal ions. Lipid peroxidation is the oxidative degradation of lipids with a number of carbon-carbon double bonds. Lipids have been associated in the pathogenesis of a number of diseases and clinical conditions like atherosclerosis, diabetes, hepatotoxicity and inflammation (Halliwell, 1991; Halliwell et al., 1992; Pietta, 2000). There are a number of flavonoids such as quercetin, myricetin, quercetin and rutin, which possess lipid peroxidation inhibitory activity (de Groot, 1994; Grace, 1994) (Letan, 1966).

In addition to the antioxidant activity, flavonoids have remarkable antimicrobial activity as well. Antiviral activity of flavonoids on various RNA and DNA viruses have been demonstrated by different groups (Kaul et al., 1985; Wang et al., 1998) . Antibacterial activity of quercetin and apigenin have been exhibited by Wu et al. (2008). Quercetin is also isolated as an active ingredient from lotus leaves in the treatment of periodontitis (Li and Xu, 2008).

Hormone-like steroids, particularly estrogen, which has neuroprotective effects on the brain, are well recognized in the prevention of many chronic illnesses. Some classes of flavonoids exhibit hormone like effects that resemble to steroid hormones (Srivastava and Bezwada, 2015). Amongst genistein, daidzein and equol which are examples of isoflavonoids have been examined for their estrogenic activity. Potential activity of these metabolites has been determined in several chronic diseases like cancer, cardiovascular disorders, and osteoporosis. Genistein exhibited the most promising activity in bone loss in postmenopausal women (Metzner et al., 2009; Wiseman, 2000).

The impact of flavonoids, notably quercetin, on a range of inflammatory pathways and immune functions were studied by Comalada et al. (2005), and it was discovered that specific flavonoids contribute to inhibit the initial stages of inflammation and boost the immune system. Flavonoids and tannins from the leaves of the plant *Spilanthes paniculata* have been shown to exhibit anti-inflammatory properties (Hossain et al., 2014).

Several studies on the anticancer activity of flavonoids such as tangeritin, 3-hydroxyflavone, 3′,4′-dihydroxyflavone, 2′,3′-dihydroxyflavone, fisetin, apigenin, luteolin, daidzein, and genistein have been conducted (Alshehri and Sharifi-Rad, 2021; Kamaraj et al., 2009; Luca et al., 2020; Sirotkin et al., 2021). Numerous phenolics such as flavonoids, tannins, stilbenes, curcuminoids, coumarins, lignans, quinones have chemopreventive characteristics and moreover they play a role in inducing apoptosis by arresting the cell cycle, regulating carcinogen metabolism, and ontogenesis expression, as shown by researchers working on natural phenolic compounds and their possible use for cancer prevention. Researchers have also suggested that flavonoids have complementary mechanisms of action, like those of antioxidant capacity and scavenging free radicals, regulation of carcinogen metabolism, modulation of gene expression on oncogenes and tumor-suppressor genes in cell growth and differentiation, induction of cell cycle arrest and apoptosis, regulation of enzyme activities in detoxification, oxidation and reduction, anti-inflammatory characteristics, and activities on other potential mechanisms (Huang et al., 2010; Ren et al., 2003).

Flavonoids and their influence on central nervous system protection are of specific importance, remarkably in neurodegenerative disease generated by the cumulative effect of oxidative stress, inflammation, and metal accumulation; a great deal of data is available. Alzheimer's disease and other dementias are examples of major neurodegenerative diseases. Flavonoids, like flavonols, have been related to decreased rates of dementia in the general population (Beking and Vieira, 2010). According to Hwang and Yen (2008) and Huang et al. (1999), citrus flavanones such as hesperidin, hesperetin, and naringenin can cross the blood–brain barrier which may be useful in the treatment of neurodegenerative illnesses. Flavonoids have also been linked to anti-aging and anti-diabetic (Meng et al., 2008; Saul et al., 2009; Waisundara et al., 2009; Zhang et al., 2009) .

Many flavonoids show chemoprevention effect against various cancer cells. The interaction mechanisms of these compounds include the estrogenic/antiestrogenic activity, prevention of oxidation, anti-inflammatory activity, regulation of the host immune system, anti-proliferation or apoptosis, induction of cell cycle arrest, induction of detoxification enzymes, and changes in cellular signaling. On the other hand, it can be reported that low stability, rapid metabolism and poor adsorption capability of the flavonoids weaken their pharmacological effects. For that reason, via nanoformulations, pharmacological effects can be improved. Due to their poor chemical stability, flavonoids can easily degrade with the effect of temperature, light, pH and radiation.

Here, we present a few examples about some of the superior properties flavonoids has gained because of nanoformulations. Nanoformulations applied to the flavonoids improves significantly the bioavailability and pharmacological potentials of the mentioned compounds. On this topic, many remarkable papers take are available in the literature. Nano-chemoprevention concept was firstly used by Siddiqui et al.(Siddiqui et al., 2009). In the mentioned study, author investigated the effect of encapsulated epigallocatechin-3-gallate (EGCG) in polylactic acid-–polyethylene glycol (PLA–PEG) nanoparticles against human prostate cancer cell. The author noted that encapsulated form is approximately 10 times more effective compared to noncapsulated form of EGCG. In another research, it was shown that the encapsulation supports the delivery and accumulation of chrysin in T47D cells and encapsulated drug

is more effective than free drug. Luo et al. explained the high cytotoxicity effect on cervical cancer of gold-quercetin nanoparticles (Luo et al., 2016). Nontoxic curcumin nanoparticles induced apoptosis in cancer cells more than free curcumin. Another study reported that the solubility of the prenylated flavonoid artocarpin was increased with a suitable nanoformulation (Tzeng et al., 2016). Silibinin is a flavonoid widely considered in the studies including anticancer activity research, but its low solubility and poor bioavailability decreases its efficiency at the tumor sites. Gohulkumar and coworkers compared the isolated (SIL) and encapsulated (SILNPs) forms of silibinin in terms of the anticancer efficiency in oral carcinoma. In the paper, it was noted that SILNP has higher cytotoxic effects than SIL (Gohulkumar et al., 2014). The encapsulated quercetin inserted to the liposomes gained higher

**Table 2**
*In vivo* studies of anti-cancer effects of flavonoids in the treatment of lung cancer.

| Phycochemical class | Phytochemials | Animal model | Carcinogen | Observation | Reference |
|---|---|---|---|---|---|
| **Flavones** | Luteolin | Nude mice | | Decrease the expression of AIM2, caspase-1, and IL-1β | (Yu et al., 2019) |
| **Flavones** | Luteolin | Nude mice | | Induce the anticancer activity of TRAIL. | (Yan et al., 2012) |
| **Flavones** | Luteolin | Swiss Albino Mice | BaP | Reduce the expression of PCNA, CYP1A1 and NF-κB | (Kasala et al., 2016a) |
| **Flavones** | Luteolin | Nude mice | | Inhibition of IFN-γ-induced PD-L1 expression | (Jiang et al., 2021) |
| **Flavones** | Luteolin | SCID mice | | Decrease proliferation marker Ki-67 and signaling marker p-Limk1/2 and p-cofilin expression | (Zhang et al., 2021) |
| **Flavones** | Apigenin | Athymic nude mice | | Increase the expression levels of DR4 and DR5 | (Chen et al., 2016) |
| **Flavones** | Apigenin | mice | | Suppress GLUT1 expression levels in skeletal muscle, white adipose tissue, the heart, brain, liver, lung, and pancreas obtained from apigenin-treated mice. | (Lee et al., 2016) |
| **Flavones** | Apigenin | Nude mice | | Inhibition of IFN-γ-induced PD-L1 expression | (Jiang et al., 2021) |
| **Flavones** | Chrysin | Swiss albino mice | BaP | Reduce expression of PCNA, COX-2 and NF-κB | (Kasala et al., 2016b) |
| **Flavones** | Baicalein | Swiss Albino Mice | BaP | Increase enzyme antioxidants and non-enzyme antioxidants, Decrease the activity of phase I enzymes, Increase the activity of phase II detoxification enzymes, Preserve pulmonary microvasculature and normal growth pattern | (Naveenkumar et al., 2012) |
| **Flavones** | Baicalein | Balb/c nude mice | | Inhibition of Id1 in an Src dependent manner. decreasing of mesenchymal markers (vimentin and N-cadherin) and increasing angiogenesis marker (VEGF) and epithelial markers (E-cadherin) | (Zhao et al., 2019) |
| **Flavones** | Baicalein | Balb/c nude mice | | Reduce expression of both 12-lipoxygenase and VEGF proteins | (Cathcart et al., 2016) |
| **Flavanone** | Hesperidin | Swiss Albino Mice | BaP | Reduce mast cell density, Down-regulate expressions of COX-2, MMP-2 and MMP-9 | (Kamaraj et al., 2010) |
| **Flavanone** | Hesperetin | Nude mice | | Inhibition of tumor growth. | (Kong et al., 2020) |
| **Flavanone** | Naringenin | Swiss Albino Mice | BaP | Activate the enzymatic antioxidants (SOD, CAT, GPx, GST) Suppress unregulated expression of CYP1A1, PCNA and NF-κB Reduce pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β) Reduce proliferative lesions in lung | (Bodduluru et al., 2016) |
| **Flavanone** | Naringenin | BALB/c mice | | Inhibition of tumor progression in mouse models of lung carcinoma (LLC) by promoting natural killer (NK) cell development and cytotoxicity against cancer. Produce an additive effect on inactivating TGF-β1/Smad3 signaling, | (Lian et al., 2018) |
| **Flavnones** | Scutellarin | BALB/c nude mice | | Up-regulate LC3-II and p-ERK1/2 level, and down-regulate p-AKT | (Sun et al., 2018) |
| **Flavnones** | Scutellarin | BALB/c mice | | Increase iodine-125- induced tumor inhibition *in vivo*. | (He et al., 2021) |
| **Flavonols** | Fisetin | Swiss Albino Mice | BaP | Restore lipid peroxidase, enzymatic and non-enzymatic antioxidants levels, Reduce the lung lesions, Reduce PCNA | (Ravichandran et al., 2011) |
| **Flavonols** | Fisetin | C57BL/6 J mice | | Inhibition of endothelial cells migration and capillary-like structure formation. Inhibition of tumor growth and angiogenesis. | (Touil et al., 2011) |
| **Flavanols** | EGCG | A/J Mice | NNK | Reduce the induction of DNMT1, Reduce phospho-histone H2AX (γ-H2AX) and phospho-AKT (p-AKT) | (Jin et al., 2015) |
| **Flavanols** | EGCG | A/J Mice | BaP | Pure EGCG administered in the diet was not an effective chemopreventive agent, likely due to preferential degradation of pure EGCG compared to EGCG present in a mixture of catechins. | (Zhang et al., 2010) |
| **Flavanols** | EGCG | BALB/c mice | | Increase the ROS generation. Suppress *ERK1/2* and *p-ERK1/2* expression | (Chen et al., 2020) |
| **Flavonols** | Quercetin | Mongolian Gerbils | BaP | Suppress the expression of *TNF-α, IL-1β*, phospho-c-Jun and phospho-JNK | (Chan et al., 2012) |
| **Flavonols** | Quercetin | Athymic nude mice | | Suppress tumor growth by inhibiting aurora B activities | (Xingyu et al., 2016) |
| **Flavonols** | Quercetin | Mice | | Has potent inhibitory activity on non-small cell lung cancer by regulating the ratio of Bax/Bcl-2. | (Li et al., 2019a) |
| **Flavonols** | Kaempferol | BALB/c nude mice | | Inhibition of the protein level of the phosphorylation of AKT, PI3K and ERK and significantly activated caspase-3 to induce tumor apoptosis. | (Kuo et al., 2015) |
| **Flavonols** | Myricetin | BALB/C nude mice | | Increase lung tumor cell killed by radiation *in vivo*, function as a powerful radiosensitizer for lung cancer. | (Zhang et al., 2014) |
| **Anthocyanidins** | Delphinidin | Athymic nude mice | | Inhibition of tumor growth, decrease in the expression of markers for cell proliferation (*Ki67* and *PCNA*) and angiogenesis (*CD31* and *VEGF*), and induction of apoptosis | (Pal et al., 2013) |

solubility and bioavailability compared to the free quercetin. As can be understood from the examples given above, nanoformulations made significantly improve the pharmacological efficiencies of flavonoids against various cancer cells.

*Toxic side effect of flavonoids*

In addition to the studies including anticancer, antioxidant, antiviral, and anti-inflammatory properties of flavonoids, the studies also explaining their toxic effects attract a great deal of attention from researchers. It is important to note that he toxic effects of these compounds should never be ignored in the possible consumption of the foods including flavonoids. The toxic effects of flavonoids observed in both *in vivo* and *in vitro* experiments is discussed below. This part presents the carcinogenicity, liver and kidney toxicity and negative effects of the flavonoids on thyroid, reproductive organs and intestinal flora. Because of such reasons, we can say that the tolerable number of flavonoids used as food supplements in foods should be carefully determined. The studies performed proved that toxicity mechanisms of these compounds are quite complicated. Some researchers noted that flavonoids are negatively associated with some cancer types (Chang et al., 2018a). A recent paper penned by Feng and coworkers explained that the risk of the breast cancer increases as the intake of total flavonoids increases (Feng et al., 2020). Some animal experiments supported that daily intake of genistein (250 mg/kg diet) enhances an aggressive type of prostate cancer (El Touny and Banerjee, 2009). It was also reported that quercetin at low concentrations increases the proliferation of the human breast cancer cell lines, MCF-7 SH and MCF-7WT (Miodini et al., 1999). This toxicity of the quercetin can be explained considering the reactive metabolites forming when quercetin oxidation happens. These metabolites have a reverse effect on DNA. There are some studies reporting the hepatotoxicity and nephrotoxicity of flavonoids in the literature. The paper published by James and coworkers presents the relation of epigallocatechin gallate (EGCG) intake with such toxicities (James et al., 2015). A series of experiments showed that hepatotoxicity of EGCG can be associated with the increasing use of green tea. Same molecule exhibits nephrotoxicity and increases the serum creatinine. Rasheed and coworkers noted that daily intake of EGCG (100 mg/kg/day) maybe cause to the increasing in deteriorated oxidative stress condition (Hard et al., 2007). Quercetin is another flavonoid associated with nephrotoxicity. In a study reported by the US National Toxicology Program (NTP) and in a paper of Hard and coworkers, it was noted that high quercetin dose triggers an increase in renal tumors (Hard et al., 2007). According to some researchers, toxic effect on thyroid of flavonoids is affected from some factors like the duration of intake and the realistic exposure conditions Many experiments *in vitro* and *in vivo* have confirmed that flavonoids affect the functions of the thyroid. It should be noted that phytoestrogens are the most effective flavonoids, acting on thyroid function and metabolism. Many papers reported that phytoestrogens and quercetin have adverse effects on the functions of thyroid (Habza-Kowalska and Kaczor, 2019). Phytoestrogens exhibit high binding affinity to estrogen receptor (ER) because of the diphenolic rings in their structures. Daidzein and genistein are among important isoflavones. It was reported that the excessive intake of the mentioned isoflavones can affect inverse effect on hormone metabolism and endocrine function (Cederroth et al., 2012). In addition to mentioned studies, Reed and coworkers reported that isoflavone intake significantly affects male reproductive hormones (Reed et al., 2021).
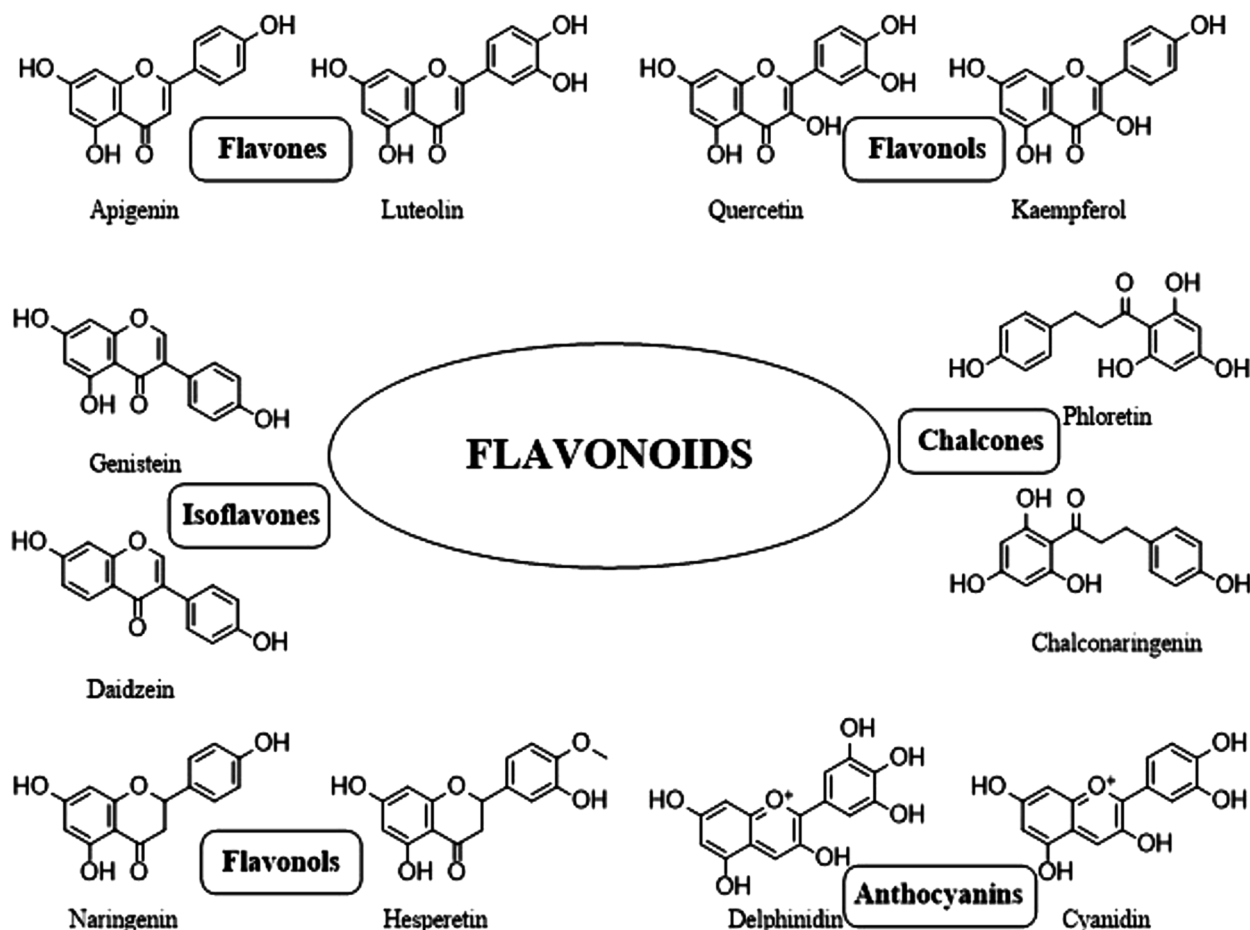


**Fig. 1.** Chemical structures of flavonoids and their classes.

## Lung cancer

### Epidemiology of lung cancer

Lung cancer is among the most common malignant tumors in the world. According to the survey published by the International Agency for Research on Cancer (IARC) of the World Health Organization in 2021, the number of lung cancer cases worldwide in 2021 by the World Health Organization was 2 206 771 in 2020 (Sung et al., 2021) . It constitutes 11.4% of new cancer cases in the world and ranks second among malignant tumors after breast cancer (11.7%). Lung cancer remains the leading cause of cancer death worldwide, with 1 796 144 deaths occurring in 2020, representing approximately 18% of all cancer deaths (Sung et al., 2021). Lung cancer is the most common type of cancer and the leading cause of cancer death in men, followed by prostate and colorectal cancer in terms of incidence and liver and colorectal cancer in terms of mortality. In women, lung cancer is the third most commonly diagnosed cancer type after breast and colorectal cancer and the second leading cause of cancer-related death after breast cancer (Sung et al., 2021).

The five-year survival rate for lung cancer (19.4%) was found to be lower than many leading cancer types such as prostate (98.8%), breast (89.8%) and colorectal (64.4%) (Howlader et al., 2019). However, when the disease is present in the lungs, the five-year survival rate is 56%, and only 16% of lung cancer cases are diagnosed at an early stage. The five-year survival rate for distant tumors (that has spread to other organs) is only 5 percent (Howlader et al., 2019).

Although smoking is closely associated with the risk of developing lung cancer, it causes an estimated 80–90% of lung cancer cases, it has been shown that only about 15% of smokers develop lung cancer, so genetic factors should be considered in this case (Spitz et al., 2003).

Smoking intensity and life expectancy affect cancer risk proportionality (Mattson et al., 1987). Other contributing factors are exposure to environmental toxicants with the inclusion of asbestos, radon, and certain metals such as arsenic, cadmium, and chromium (Field and Withers, 2012). Exposure to asbestos creates a synergistic effect with tobacco use, and both risk factors have been found to be associated with higher lung cancer rates than use alone. It has also been reported that exposure to organic chemicals in coal smoke and burning fuel are risk factors for lung cancer (Loomis et al., 2013). Presence and family history of chronic obstructive pulmonary disease are associated with lung cancer even after limiting tobacco exposure (Alberg et al., 2013).

### Types of lung cancer

Lung cancer is a heterogeneous disease consisting of pathologically and clinically significant subtypes (Fujimoto and Wistuba, 2014; Travis et al., 2013a, 2013b). According to the main histotype, prognostic and therapeutic effects, lung cancers are divided into two main groups: small cell lung carcinoma (SCLC, 12.9% of the cases) and non-small-cell lung carcinoma (NSCLC, 83.9% of the cases) being the latter the most common. (Fujimoto and Wistuba, 2014; Sung et al., 2021).

***Small cell lung carcinoma*** is the most aggressive and rapidly growing of all lung cancer types and is known to be strongly associated with smoking (Govindan et al., 2006). Other risk factors for the development of SCLC include exposure to halogenated ethers, asbestos, arsenic, radon, chromium, polyaromatic hydrocarbons and vinyl chloride. It has been suggested that female smokers are more likely to develop SCLC than their male counterparts, but the reasons for this have not yet been fully elucidated (Govindan et al., 2006). SCLCs metastasize rapidly to many sites in the body and are usually detected after they have spread widely (Legato, 2010).
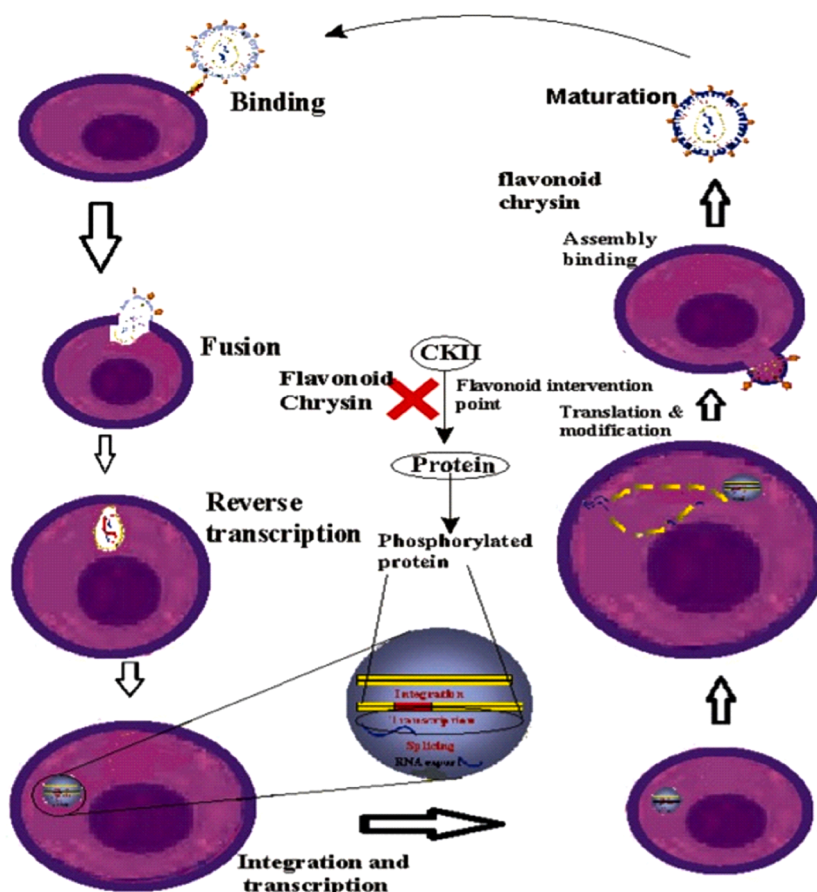


**Fig. 2.** Carcinogenesis stages and potential effect of flavonoids in cancer progression.

***Non-small-cell lung carcinoma*** has three main types based on the type of cell found in the tumor: Non-squamous cell lung cancer also known as adenocarcinoma (ADC), squamous cell lung carcinoma (SqCC) and large-cell (undifferentiated) lung carcinoma (LCLC) (Beasley et al., 2005). Other types, including salivary gland-type tumors, sarcomatoid carcinomas, and others, account for a very small proportion of total NSCLC cases (Rodriguez-Canales et al., 2016a).

***Non-Squamous cell lung carcinoma (Adenocarcinoma)*** is the most common type of NSCLC and accounting for the 47.9% of lung cancer cases (Howlader et al., 2019). Although adenocarcinomas, like other lung cancers, are associated with smoking, this cancer type occurs also in non-smokers (especially women) who develop lung cancer (Rodriguez-Canales et al., 2016a). ADC is defined as a malignant epithelial tumor with glandular differentiation indicating mucin production identify by mucin staining like mucicarmine or expression of pneumocyte marker such as napsin A or thyroid transcription factor 1 (TTF1) (Travis et al., 2015). Generally, ADC arise in the outer, or peripheral, areas of the lungs (Russell et al., 2013, 2011; Shimosato et al., 1980). They also tend to spread to the lymph nodes and beyond.

***Squamous cell lung carcinoma*** accounts for 23.2% of all lung cancers (Howlader et al., 2019). SqCC usually occurs in a central location originating from the main or lobar bronchus (Travis et al., 2015). Histologically, SqCC is defined by the World Health Organization (WHO) as a malignant epithelial tumor that displays keratinization and/or intercellular bridges or expresses immunohistochemical (IHC) markers (p40 or p63 and cytokeratins 5/6) of squamous cell differentiation (Travis et al., 2015). This type of lung cancer mostly stays in the lung, spreads to the lymph nodes, and becomes quite large, forming a cavity (Rodriguez-Canales et al., 2016a).

***Large-cell lung carcinoma*** is the least common type of NSCLC, accounting for 1.5% of all lung cancers (Howlader et al., 2019). LCLC is defined as an undifferentiated NSCLC carcinoma, which does not show histological or IHC evidence of squamous cell, glandular, or small-cell differentiation (Travis et al., 2015). This type of cancer has a high tendency to spread to lymph nodes and distant sites. Other types of cancer may occur in the lung; these types are much less common than NSCLC and SCLC and together account for only 5.2% of lung cancers (Howlader et al., 2019).

*Treatment of lung cancer*

According to the 2020 and 2021 updates of the current NCCN Guidelines on targeted therapies, immunotherapies, and their respective biomarkers for patients with NSCLC, several new targeted therapies (or new indications for treatments), including capmatinib, lorlatinib, prasetinib, selpercatinib, and fam-trastuzumab deruxtecan, are now recommended for patients with certain metastatic NSCLC who have specific actionable biomarkers (Ettinger et al., 2021) (Gainor et al., 2020; Shaw et al., 2020; Smit et al., 2020; Tsurutani et al., 2020; Wolf et al., 2020). In general, lung cancer treatment includes a variety of medical treatments such as surgical resection, chemotherapy, and radiation. Surgical resection is the preferential treatment for early-stage lung cancer (Howington et al., 2013). Adjuvant chemotherapy is recommended for completely resected stage III NSCLC encompassing a heterogeneous patient group. Patients with limited nodal (N1) involvement may be candidates for prior surgical resection followed by chemotherapy and/or radiation (Nasim et al., 2019). Patients with more advanced nodal (N2) involvement are generally recommended to undergo surgery only after induction therapy, as better outcomes are achieved (Ramnath et al., 2013). Patients with the most advanced nodal (N3) involvement usually do not undergo surgery (Nasim et al., 2019). Platinum-based 2-drug chemotherapy such as cisplatin and carboplatin is standard for patients with stage IV NSCLC, but in addition, the last few years have made important additional therapies for certain driver mutations possible (Socinski et al., 2013). These mutations are considered inducible oncogenic drivers (*i.e.* treatable with certain drugs) as they cause certain subclasses of NSCLC and can therefore be targeted with selective inhibitors. Important actionable mutations play important roles in both
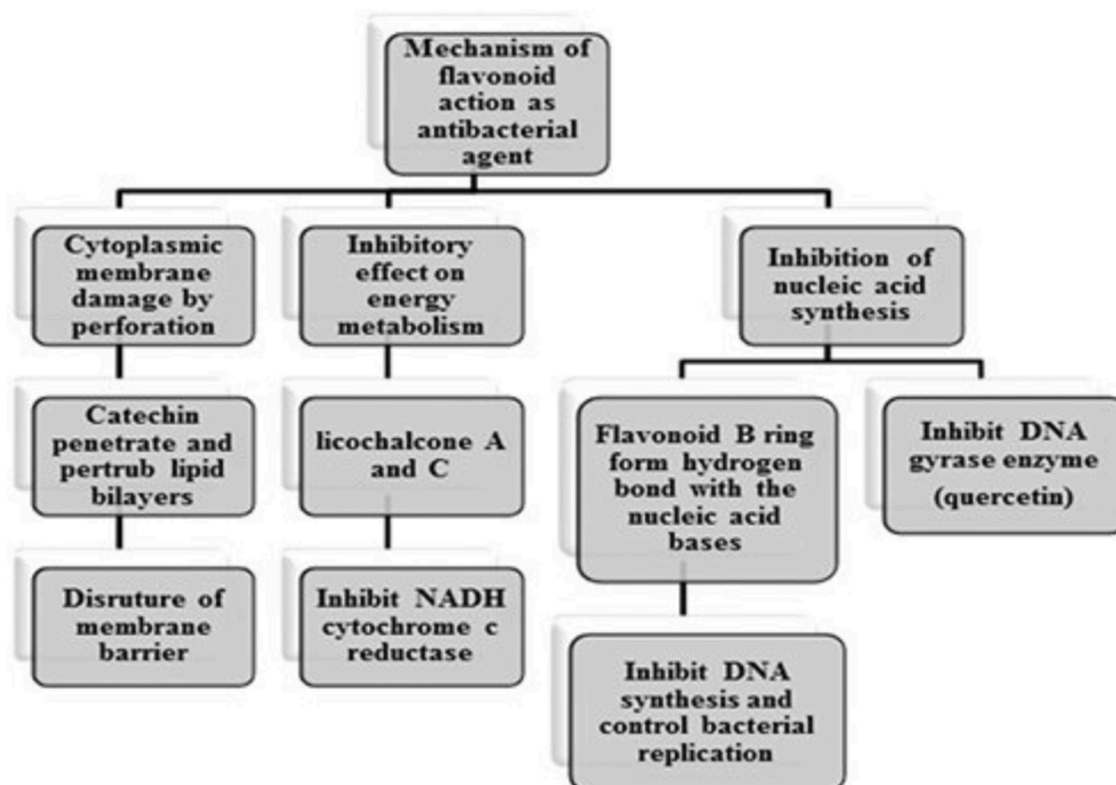


**Fig. 3.** Different ways of flavonoid action on bacterial cells.

biological mechanisms and clinical susceptibility to lung cancer therapy and these are: in non-squamous cell lung carcinomas: *EGFR, EML4-ALK* (Echinoderm microtubule associated protein-like protein 4 fused with Anaplastic Lymphoma Kinase), *KRAS* (Kirsten rat sarcoma viral oncogene homolog), *MET* (mesenchymal-epithelial transition factor), *ROS1* (c-ros oncogene 1), *RET* (rearranged during transfection), *BRAF* (v-Raf murine sarcoma viral oncogene homolog B1), and *TP53* (tumor suppressor protein 53) and in squamous cell lung carcinomas: *FGFR1* (fibroblast growth factor receptor 1), *PIK3CA* (phosphoinositide-3-kinase catalytic subunit alpha isoform), *DDR2* (discoidin domain receptor 2), *MET, SOX2* (SRY related HMG box gene 2), *PTEN* (phosphatase and tensin homolog), *CDKN2A* (TP53 and cyclin-dependent kinase inhibitor 2A) (Collisson et al., 2014; Hammerman et al., 2012).

Lung cancer is known to be associated with *PI3K/Akt* (phosphatidylinositol-3-kinase/ protein kinase B), *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) and *TP53* (tumor protein 53) mutations (Vigneswaran et al., 2016), *RTK* alteration (receptor of tyrosine kinase) including *EGFR* (epidermal growth factor receptor), *ROS1* (reactive oxygen species), c-MET, RET (proto-oncogene tyrosine-protein kinase receptor) and *ALK* (anaplastic lymphoma kinase) (Park et al., 2017). These genetic changes affect multiple cellular functions which include cell proliferation, growth, survival, differentiation, motility, invasion and intracellular signaling. Screening for reactive oxygen species proto-oncogene-1 gene rearrangements, epidermal growth factor receptor gene mutations, *KRAS proto-oncogene* (KRAS, Kirsten rat sarcoma 2 viral oncogene homolog) point mutations, *B-raf* proto-oncogene point mutations and anaplastic lymphoma kinase gene rearrangements for molecular detection of tumor tissue is the approach that is usually used, because the presence or absence of such genetic changes can predict the response to certain agents and contribute to the implementation of targeted therapies. (Nasim et al., 2019; Rodriguez-Canales et al., 2016a). In addition, treatment with immunotherapies can be applied by selecting tests to determine the expression levels of programmed death ligand-1 (Nasim et al., 2019).

SCLC is characterized by rapid doubling time, high growth fraction, and early development of diffuse metastases. The NCCN Guidelines Opinions focus on recent updates on immunotherapy, systemic therapy, and radiation therapy (RT) for patients with SCLC (Kalemkerian et al., 2018). SCLC is treated with a simplified approach compared to NSCLC; all patients receive systemic therapy (Nasim et al., 2019). Patients with confirmed limited-stage disease also receive radiation. Surgical resection is performed for less than 5% of all SCLC with stage I disease confirmed by invasive nodal staging and PET (Positron emission tomography) scan (Nasim et al., 2019). In addition, adjuvant postoperative chemotherapy is given. Prophylactic cranial irradiation is generally recommended as it provides a survival advantage to all patients who respond to therapy (Jett et al., 2013).

Despite all these interventions, lung cancer-related deaths have become more difficult to control or prevent. These traditional approaches, which include various medical treatments such as surgical resection, chemotherapy, and radiation, lack precision and provide minimal amounts of therapeutic drugs (due to their lipophilic nature and high first pass metabolism). In addition, most of the chemotherapeutics cause side effects by acting on normal tissues due to their non-targeting nature (Ahmad et al., 2015a). Therefore, identifying treatable oncogenic changes associated with cancer formation has been the primary goal of cancer research and has led to the search for newer targeted therapeutic approaches.

### Anticancer properties of flavonoids in lung cancer

Phytochemicals are plant-derived natural compounds used in the treatment of various diseases, especially in cancer. There are many studies showing its effects on tumor cell proliferation, growth and metastasis (Budisan et al., 2017; Vauzour et al., 2010). Flavonoids are the most common and widely distributed group of plant phenolics

derived from natural sources especially fruits, vegetables, and seeds (Harborne and Williams, 2000). Flavonoids show numerous beneficial effects on human health and are important for the design of new therapeutic agents for a variety of diseases, including lung cancer. The biological action of flavonoids is mainly to inhibit the production of reactive oxygen species (ROS), and this capacity can alter a wide variety of essential cellular processes that affect various molecular mechanisms in tumor cells (Batra and Sharma, 2013; Budisan et al., 2017). These mechanisms include modulation of cell signaling pathways and inhibition of activation of key transcription factors. In addition, specific cell cycle arrest, activation of apoptosis and modulation of carcinogen metabolizing enzymes are among these mechanisms (Braicu et al., 2017; Khan and Mukhtar, 2015). These mechanisms are directly related to the inhibition of lung cancer development or progression. The anti-cancer properties of flavonoids, which affect various molecular mechanisms in tumor cells, have been demonstrated by many *in vitro* and *in vivo* studies. It is summarized in Tables 1 and 2. By interfering with key regulatory effectors, flavonoids can affect tumor growth resulting from high cell division rate and/or reduction in cell death rate (Fig. 4). With studies proving direct binding and molecular modeling, flavonoids are recognized in the literature as protein kinase inhibitors for cancer (Hou and Kumamoto, 2010; Regad, 2015). The effects of flavonoids on kinase function may be independent of their main activity as antioxidant effects, but may also be related to the reactive oxygen species (ROS) activated MAPK (mitogen-activated protein kinase) cascade, PI3K (phosphatidylinositol 3-kinase)/Akt (serine/threonine kinase 1) or Janus kinase/signal converters and activators of transcription (JAK/-STAT) pathways (Cao et al., 2016; Shanmugam et al., 2016; Zhang et al., 2018b) (Fig. 4).

It has been suggested that targeting the PI3K/Akt pathway by important representatives of the flavonoids apigenin and lutein may be an important therapeutic tool for overcoming clinical problems associated with lung cancer tumor heterogeneity and acquired resistance (Zhang et al., 2018b; Zhou et al., 2017). Lutein inhibits the PI3K/Akt signaling pathway, causing decreased cell proliferation and activation of apoptosis in lung cancer cells (Zhang et al., 2018b), while apigenin was a novel AKT inhibitor in lung cancer that suppresses Akt phosphorylation, and inhibited *MMP-9* (matrix metalloproteinases-9), *HEF1* (human enhancer of filamentation 1) and *GSK-3* (glycogen synthase kinase-3) gene expression (Zhou et al., 2017). As a result of *in vivo* studies, it was concluded that apigenin reduces cell proliferation and induces apoptosis in lung cancer (Chen et al., 2016; Jiang et al., 2021). In addition, glucose metabolism in cancer cells is another important phenomenon to be investigated, and although some studies did not conclude that apigenin directly changes glucose metabolism in cancer cells, they also obtained the result that it suppresses the *GLUT1* expression level in apigenin-treated mice (Lee et al., 2016).

JAK-STAT3 signaling is activated by the action of targeting downstream cytokine receptors, with an effect on a wide variety of cellular functions associated with MAPK effectors, Akt, or proteins regulated by the cell death mechanism such as proapoptotic protein BAD or caspases promoting cell survival (Hou and Kumamoto, 2010). It was found that after the application of Quercetin, another flavonol member, to A549 and NCI-H358 NSCLC cells, there were significant increases in apoptotic cell population and caspase-3 activity in a time- and dose-dependent manner, resulting in MMP loss (Cincin et al., 2014). Similar results were obtained as a result of *in vivo* studies supporting *in vitro* studies. In a study with mice, they obtained the result that quercetin has a strong inhibitory activity on non-small cell lung cancer by regulating the Bax/Bcl-2 ratio (Li et al., 2019). Similarly, in other studies with mice, it was stated that quercetin reduced lung cancer growth and increased the number of cells leading to apoptosis (Chan et al., 2012; Xingyu et al., 2016). Treatment of Naringenin, a flavanone member, has been shown to cause significant changes in lung cancer cell proliferation through inhibition of AKT and MMP2/9 activities in a dose-dependent manner (Chang et al., 2017). In a study supporting the in-vitro study, they
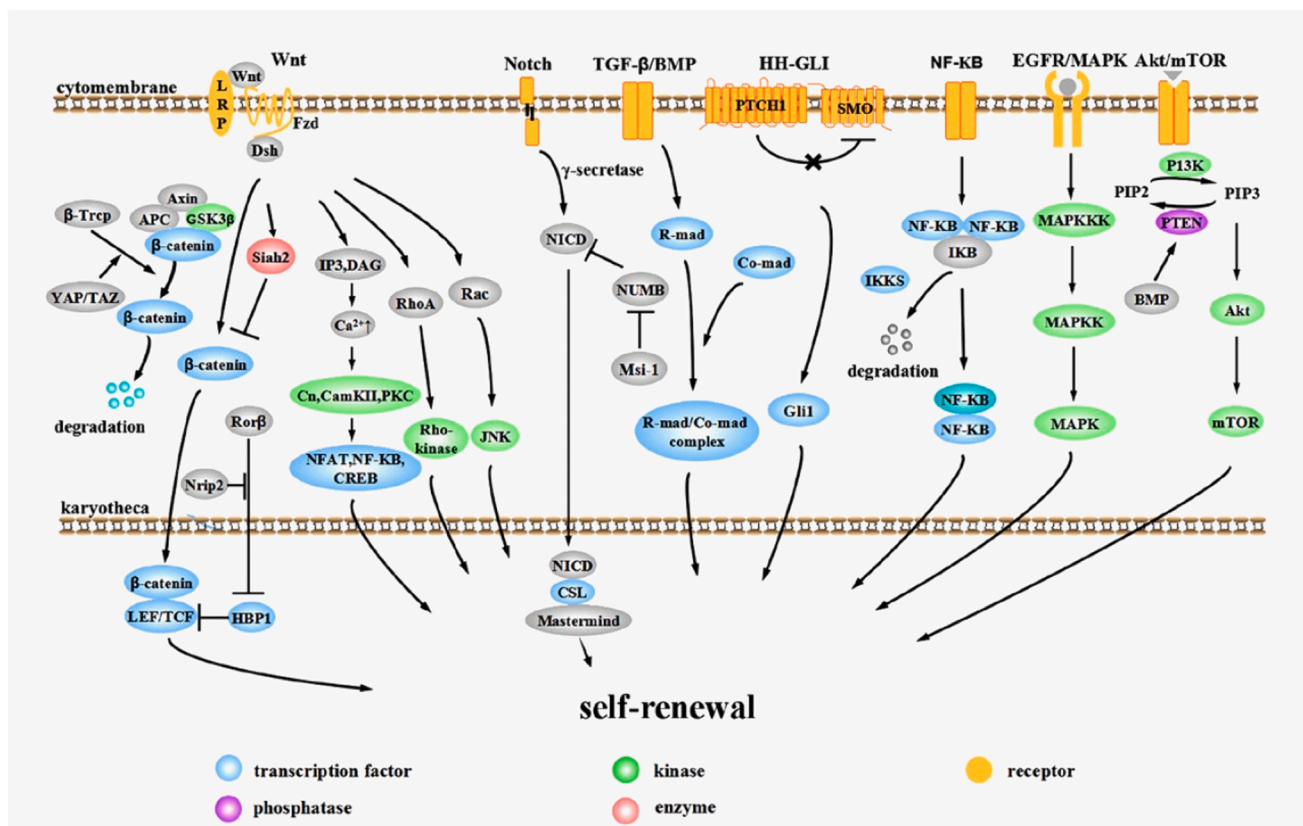
**Fig. 4.** Modulation of cellular signaling pathways by flavonoids targeting multiple cellular components altered in lung cancer protein kinase C (PKCs) via integrin, which plays a major role in the regulation of cancer cell proliferation and cellular adhesion (Zanoaga et al., 2019).

concluded that Naringenin, which acts as a Smad3 inhibitor, effectively inhibits tumor progression in mouse models of lung cancer (LLC) by promoting natural killer (NK) cell growth and cytotoxicity against cancer. Furthermore, they concluded that treatment with NG produced an additive effect on inactivating TGF-β1/Smad3 signaling and therefore suppressed lung carcinoma growth by promoting NK cell immunity against cancer through an Id2 and IRF2-related mechanism (Lian et al., 2018). In another study, it was shown that naringenin activated enzymatic antioxidants (SOD, CAT, GPx, GST), suppressed the dysregulated expression of *CYP1A1, PCNA* and *NF-kB*, decreased proinflammatory cytokines (TNF-α, IL-6 and IL-1β) and thus reduced the proliferative lung lesions (Bodduluru et al., 2016). Kaempferol, the flavonol member of the flavonoids, reduced claudin-2 expression in A549 cells through inhibition of the interaction between STAT3 and the promoter region of claudin 2, which showed kaempferol can directly block the interaction of STAT3 on DNA (Sonoki et al., 2017).

MAP4K3 (Mitogen activated protein kinase 3), an important modulator of cell growth and autophagy in mammals, is another important protein kinase (Hammond et al., 2010). Li et al. (2021a) reported that baicalein may cause inactivity of MAP4K3, possibly by binding directly to the substrate binding site of this kinase domain, MAP4K3. They also suggested that baicalein might induce the degradation of *MAP4K3* by reducing its stability and promoting the ubiquitin proteasome pathway, thereby triggering autophagy, causing the decreasing/ending proliferation of lung cancer cells (Li et al., 2021a). Additionally, *in vitro* studies have shown that baicalein reduces mesenchymal markers (vimentin and N-cadherin) and angiogenesis markers (*VEGF*) and epithelial markers (*E-cadherin*), thus playing an important role in the EMT, migration and angiogenesis process in targeted mouse models (Zhao et al., 2019). A similar study was conducted by Cathcart et al. (2016) and they obtained similar results.

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of the mammalian target of rapamycin (mTOR) pathway plays a various role in cell proliferation, survival, differentiation, motility, adhesion and invasion (Beck et al., 2014; Fumarola et al., 2014). It has been reported that after scutellarin treatment, it suppresses the proliferation of A549 cells, triggers apoptosis, and there is significant increase in arrest in the G0/G1 phase. It has also been reported that the ratio of BAX/BCL-2 and cleaved (active) caspase-3 increases and activates the scutellarin, AKT/mTOR/4EBP1 and STAT3 pathways (Cao et al., 2019). These study results supported the study results in mouse models. It was found that 30, 60 mg/kg scutellarin treatment could up-regulate *LC3-II* and *p-ERK1/2* level, and down-regulate *p-AKT* (Sun et al., 2018). Eriodictyol, another flavonoid member, has been reported to cause apoptosis induction by regulating the Bcl-2/Bax signaling pathway and cell cycle arrest of human lung cancer A549 cells in G2/M phase. In addition, eriodictyol has also been observed to effectively inhibit the mTOR/-PI3K/Akt signaling pathway in a dose-dependent manner (Zhang et al., 2020b). In another study by Kim et al. (2017), they found that Delphinidin suppressed *CoCl₂*- and *EGF*-induced hypoxia-response element (HRE) promoter activity and specifically decreased the CoCl₂- and EGF-induced HIF-1 alpha protein expression by blocking the ERK (extracellular signal-regulated kinase) and PI3K/Akt/mTOR/p70S6K signaling pathways. They suggest that delphinidin has a potentially new role in anti-angiogenic action by inhibiting *HIF-1-alpha* and *VEGF* (Vascular endothelial growth factor) expression (Kim et al., 2017). Therefore, flavonoids are also known to play an important role in epithelial-to-mesenchymal transition (EMT) and cell migration and invasion. These results were also supported by *in vivo* study results (Pal et al., 2013). In a study on the effect of apigenin on lung cancer cells, inhibition of migration/invasion through suppression of Snail/Slug-mediated EMT was observed (Chang et al., 2018b). EGCG (Epigallocatechin gallate) has been reported to have the capacity to inhibit transforming growth factor (TGF) induced by the EMT

mechanism and inhibition of the phosphorylated form of Smad2 and ERK1/2 (Liu et al., 2012). In another study, EGCG treatment in A549 lung cancer cells determined TGF 1-mediated EMT inhibition by suppressing the acetylation of Smad2 and Smad3 (Ko et al., 2013). In A549 and H1299 cells, Baicalein, another flavonoid member, showed that it down-regulated Notch1 and hes-1 expression and significantly inhibited cell invasion and EMT (Su et al., 2018).

Activating KRAS mutations are frequently observed in NSCLC (Bar-Sagi et al., 2020; Choi et al., 2019). Increasing evidence suggests that PD-L1 expression in lung cancer is associated with KRAS signaling pathways and is intrinsically upregulated with activation downstream of KRAS signaling pathways. (Liu et al., 2020b). Immune checkpoint inhibitors target the PD-1/PD-L1 pathway to stimulate immune cells to destroy cancer cells in a variety of cancers and have been found to improve response rates and overall survival of patients with NSCLC (Liu et al., 2020b). Moreover, some clinical studies have provided data that the effects of PD-1/PD-L1 inhibitors on KRAS-mutant NSCLC are closely related to the regulation of the tumor microenvironment (Liu et al., 2020b; Wang et al., 2020). Keytruda, an FDA-approved PD-1 inhibitor for the treatment of advanced NSCLC with high PD-L1 expression, provided better results in these patients (Raedler, 2015). Recent clinical trials have demonstrated that PD-1/PD-L1 blockade therapy exerts its anti-cancer effect through modulation of the tumor microenvironment (Abril-Rodriguez et al., 2020; Li et al., 2019b; Trefny et al., 2020; Waldman et al., 2020). The presence of activating CD8+T cells in KRAS mutant patients was found to be positively associated with improved prognosis (Koyama et al., 2016; Menares and Gálvez-Cancino, 2019; Wang et al., 2019). The potential anti-cancer effects of flavonoids in the treatment of various tumors have received widespread attention (Liskova et al., 2020). Studies have shown that apigenin and luteolin have anti-cancer properties *in vivo* and *in vitro* (Adamczak et al., 2020; Couture et al., 2020). Apigenin has been found to have a much greater inhibitory effect than luteolin on many types of tumor cell lines with KRAS activating mutations (Ferino et al., 2020). Luteolin and apigenin have both been shown to suppress cancer cell growth and induce apoptosis of multiple types of malignancies (Salehi et al., 2019). There is increasing interest in apigenin and luteolin for cancer treatment as apigenin has the potential to overcome resistance to chemotherapy (Sudhakaran et al., 2019; Yan et al., 2017). However, the effects and underlying mechanisms of luteolin or apigenin combined with anti-PD-1 antibody on PD-L1 expression and anti-tumorigenesis in KRAS mutant lung cancer have not yet been fully elucidated. In a study by Jiang et al., both luteolin and apigenin showed potent anti-cancer activities *in vivo* in the H358 xenograft and Lewis lung carcinoma model and increased infiltration of T cells into tumor tissues after treatment with monoclonal PD1 antibody. They also found that apigenin showed anti-tumor activity in GM KRASLA2 mice. Thus, they concluded that both apigenin and luteolin suppressed KRAS mutant proliferation and lung cancer and down-regulated IFN-γ-induced PD-L1 expression. They suggested that treatment with PD-1 blockade and apigenin/luteolin combination has a synergistic effect and could be a prospective therapeutic strategy for KRAS mutant NSCLC (Jiang et al., 2021).

It has been demonstrated in literature studies that flavonoids play important roles by targeting cancer metabolism by modulating the expression of MicroRNAs (miRNAs) in various types of cancer, and research continues. The miRNAs modulating by flavonoids are candidates to be an important marker in the discovery of new treatment methods for many cancer types. miRNAs are a family of small endogenous non-coding RNAs that regulate post-transcriptional gene expression and are involved in a variety of biological events, including carcinogenesis (Singh et al., 2021). miRNA functions as an oncogenic or tumor suppressor under cancerous conditions (Peng and Croce, 2016; Srivastava et al., 2015b). The characteristic patterns of miRNAs have been observed in various cancer tissues, which are useful in the prognosis, diagnosis and treatment of cancer (Cho, 2010; Du and Pertsemlidis, 2010; Lee et al., 2011; Lin et al., 2010). The fact that flavonoids

play an important role in miRNA modulation demonstrates their selectivity and importance as regulators of carcinogenesis. The effects of flavonoids on the modulation of miRNA expression and the target gene names and levels associated with lung cancer are shown in Table 1. Flavonoids target cancer properties by modulating the expression of miRNAs in various types of cancer. Naringenin, calicosine, baicalin, and EGCG reduce cancer cell proliferation by modulating the expression of *miR-25–5p, miR-17–3p, miR-23a, miR-155–5p, miR- 151a, miR-10a, miR-30c, miR-31, miR-205* and *miR-17, miR-95,* (Chen et al., 2015; Curti et al., 2017; La et al., 2019; Tao et al., 2018). Similarly, quercetin, kaempferol, silymarin, EGCG, genistein, naringenin, naringin, emodin, morin, baicalein, and nobiletin are reported to modify the proliferation, invasion and metastasis of lung cancer cells by targeting miRNAs (Bhardwaj and Mandal, 2019; Chen et al., 2018; Du and Pertsemlidis, 2010; Han et al., 2018; Lu et al., 2018; Ren et al., 2016; Singh et al., 2016; Sonoki et al., 2015; Wang et al., 2011; Zhou et al., 2014).

Many studies in the literature have revealed that flavonoids have the capacity to strengthen the anticancer potential in many cancer cases (Brito et al., 2015) and to protect normal cells from the side effects that are a result of radiotherapy and chemotherapy (Falcone Ferreyra et al., 2012). These studies on the valuable effects of flavonoids in combination with chemotherapeutic and radiotherapy treatment in lung cancer have achieved promising results for cancer treatment. In this context, a combination therapy of quercetin and gemcitabine has been shown to have significant antiproliferative and pro-apoptotic activities in lung cancer cells through downregulation of *HSP70* (70 kilodalton heat shock proteins) expression (Lee et al., 2015). On the other hand, after the combined treatment of fisetin, a flavonol member, with paclitaxel on A549 cells, no correlation was observed between autophagic and apoptotic cell death, since the percentage of apoptotic cells did not increase significantly (Klimaszewska-Wisniewska et al., 2016). Genistein, which is an isoflavone, has been found to induce apoptosis due to decreased plasmic Bcl-xL levels as a result of its treatment to lung cancer cells, thus increasing the radiosensitivity of lung cancer cells. (Zhang et al., 2018c). Similarly, another study demonstrated that kaempferol can increase the radiation killing of tumor cells *in vivo*. It was concluded that phosphorylation of AKT, PI3K and ERK from tumor tissue further inhibited protein level following treatment with kaempferol plus radiation and significantly activated caspase-3 to induce tumor apoptosis. Thus, kaempferol is thought to act as a potent radiosensitizer (Kuo et al., 2015). In another study, it was found that myrcetin increased the lung tumor cell killed by radiation *in vivo* and functions as a potent radiosensitizer for lung cancer (Zhang et al., 2014). Baicalein, a flavone, was observed to increase the sensitivity of cisplatin in lung cancer cells via EMT mediated by the PI3K/Akt/NF-κB pathway (Yu et al., 2017). In another study, they concluded that the combined treatment of diosmetin and paclitaxel synergistically suppressed lung cancer cells, ROS accumulation resulting from disruption of the PI3K/Akt/GSK-3/Nrf2 pathway (Chen et al., 2019). In a study by Xu et al. (2017), they observed that the effects of baicalin and cisplatin on proliferation inhibition showed a synergistic effect for both A549 and A549/cisplatin cells. They found that A549/cisplatin cells had significantly higher levels of *MARK2* mRNA and expression of MARK2 and p-Akt protein. Thus, they found that baicalin and cisplatin had a synergistic effect in inhibiting the proliferation and invasion of human lung cancer cells in the presence or absence of cisplatin resistance (Xu et al., 2017). Combination of EGCC and cisplatin enhanced cisplatin sensitivity in lung cancer cells and caused a decrease in AXL and TYRO3 receptor tyrosine kinases (Jiang et al., 2016; Kim et al., 2009). Combination treatment of apigenin with cisplatin has been shown to cause significantly greater S phase prolongation and G2/M cell cycle arrest and apoptosis (Yan et al., 2020). In another study, they obtained lung cancer stem cells by using CD133 surface marker in non-small cell lung cancer (NSCLC) A549, H1299 cells and cisplatin-resistant NSCLC A549R cells. The cytotoxic effect of apigenin suppressed their growth in A549, H1299 and A549R CD133 positive cells treated with cisplatin, and they found that cisplatin

increased its antitumor effect. Furthermore, they observed that the synergistic antitumor effect of apigenin and cisplatin was blocked by the addition of p53 inhibitor Pifithrin-a and siRNA targeting the *p53* gene in A549R cells. Therefore, they suggested that apigenin could abolish lung cancer stem cells and increase the antitumor effects of cisplatin in NSCLC via p53 (Li et al., 2021b). In another study, they investigated the effects of human lung adenocarcinoma A549 and A549/cisplatin cells treated with different concentrations of hesperetin and cisplatin. In addition, they investigated the effects of hesperetin on A549/cisplatin cell growth *in vivo* by constructing a xenograft model of lung cancer in nude mice. Their results showed that hesperetin sensitized A549/cisplatin cells to cisplatin, and *in vivo*, hesperetin pretreatment significantly inhibited tumor growth (Kong et al., 2020). Furthermore, scutellarin also promoted cisplatin-induced cytotoxic autophagy, downregulated expression of p-AKT and c-met. *In vivo*, the co-treatment of cisplatin and scutellarin notably reduced the tumor size when compared with cisplatin treatment alone. Notably, scutellarin significantly reduced the toxicity generated by cisplatin in tumor-bearing mice (Sun et al., 2018).

The anti-cancer properties of flavonoids have received much attention, as evidenced by the large number of articles published in recent years. Many of the beneficial effects of flavonoids have been demonstrated in cancer therapy by altering the oncogenic signal, including lung cancer. It has been clearly demonstrated that flavonoids have an important role in inhibiting the growth of tumor cells, inducing apoptosis and in epithelial-mesenchymal transition (EMT) and cell migration and invasion in preclinical studies. The lack of biomarkers and gaps in our understanding of the pathogenesis of lung cancer, as well as good models for risk estimation, limit the use of flavonoids in clinical trials. The use of flavonoids in combination with chemotherapeutic and radiotherapy treatment in lung cancer has shown promising results for cancer treatment (Li et al., 2021b; Kong et al., 2020; Yan et al., 2020; Chen et al., 2019; Sudhakaran et al., 2019; Sun et al., 2018; Zhang et al., 2018c; Yan et al., 2017; Xu et al., 2017; Jiang et al., 2016; Klimaszewska-Wisniewska et al., 2016; Kuo et al., 2015; Lee et al., 2015; Zhang et al., 2014; Kim et al., 2009). When all these findings are evaluated, it can be thought that the use of flavonoids together with chemotherapeutic and radiotherapy treatment in lung cancer may create a synergistic effect and it may be more beneficial to use in clinical studies for cancer treatment in the future, therefore it may be a prospective therapeutic strategy.

**Conceptual density functional approach in cancer research**

In cancer research, the highlighting of the nature of the interactions between molecules and determination of drug-target interaction mechanisms are very important and challenging topics. In the line with these purposes, theoretical and computational approaches are widely preferred by cancer researchers. These approaches based on some important theories and principle provides useful information in especially in the design and synthesis of new anticancer drugs against various cancer types. To obtain more accurate and reliable results, within the framework of recent developments in biotechnologies and software engineering, comprehensive and innovative computational and theoretical approaches have been imparted to science. In the first stage of this part, we will provide required information about important electronic structure principles and chemical reactivity parameters, which are widely considered in cancer research and the developments of novel anticancer drugs.

Many papers including the use of Conceptual Density Functional Theory (Islam and Kaya, 2018) in cancer research are available in the literature. Conceptual Density Functional Theory (CDFT) introduced by Prof Parr and his team with the help of Density Functional Theory, which won Walter Kohn the Nobel Prize is widely preferred in the local and global reactivity analysis of molecules. In CDFT, well-known reactivity descriptors like chemical potential ($\mu$), electronegativity ($\chi$),

chemical hardness ($\eta$) and chemical softness ($\sigma$) are mathematically given as: (Kaya and Kaya, 2015a)

$$\mu = -\chi = \left[\frac{\partial E}{\partial N}\right]_{\nu(r)} = -\left(\frac{I+A}{2}\right) \tag{1}$$

$$\eta = \frac{1}{2}\left[\frac{\partial^2 E}{\partial N^2}\right]_{\nu(r)} = \frac{I-A}{2} \tag{2}$$

$$\sigma = 1/\eta \tag{3}$$

In the given formulae, E, N and $\nu(r)$ represent the total electronic energy, the total number of electrons and external potential, respectively. I and A are ground state ionization energy and electron affinity, respectively. It is important to note that Koopmans Theorem (Koopman, 1934) appearing as a strong bridge between Molecular Orbital Theory and Conceptual Density Functional Theory is widely considered in the approximately prediction of ionization energy and electron affinities of molecular systems.

One of the most striking studies showing the relation with health sciences of Density Functional Theory was penned by Maynard, Huang, Rice and Cowell (Maynard et al., 1998). In the mentioned paper, the authors investigated the reaction with some electrophilic agents of the human immunodeficiency virus type 1 (HIV-1) nucleocapsid protein p7 (NCp7) via theoretical and experimental analyses. The analyses made considering HSAB Principle provided the obtaining of important correlations between rate of reactions and softness of electrophile. The authors noted that $\chi^2/\eta$ ratio of an electrophile is a quantity regarding to its ability to promote a covalent reaction. Considering experimental and theoretical observations in the study of Maynard and coworkers, Parr, Szentpaly and Liu (Parr et al., 1999) introduced the electrophilicity index ($\omega$) via the following equation as the ratio of the square of the electronegativity of a chemical species to twice its hardness.

$$\omega = \chi^2/2\eta = \mu^2/2\eta \tag{4}$$

Polarizability ($\alpha$) is one of the fundamental properties providing useful hints about the chemical reactivity or stabilities of chemical species. This fundamental property is closely related with the chemical hardness. Some researchers attempted to predict the molecular polarizability ($\alpha_M$) in terms of the polarizabilities ($\alpha_i$) of the atoms forming the molecule via the following equation (Blair and Thakkar, 2013).

$$\alpha_M = \sum_{i=1}^{N} \alpha_i \tag{5}$$

Here, N and $\alpha_i$ are the number of the atoms in the molecule and free atom polarizability, respectively. Another molecular polarizability equation given below has been proposed through a dressed atom additive model.

$$\alpha_M = \sum_{i=1}^{N} \alpha_i^d \tag{6}$$

In the equation, $\alpha_i^d$ stands for the effective polarizability including the effect of molecular environment of an atom.

We can divide the carcinogenesis into four phases as: initiation, promotion, progression, and metastasis. It should be noted carcinogenic chemical species can lead to the onset of cancer by influencing the responsible genes for DNA repair, cell growth, apoptosis, and cell-cycle control. Some carcinogenic matters interact directly with DNA while some compounds turn into the reactive systems that can easily interact with DNA through covalent adducts causing important mutations in the responsible genes from important biological processes. As can be understood from this information, chemical reactivity analysis should be one of the essential topics of cancer research. For that reason, we will mention below from electronic structure principles and guiding rules regarding to the important descriptors like hardness, polarizability and

electrophilicity in CDFT.

*Electronic structure rules*

With the help of the observations regarding to the reactions between Lewis acids and bases, R.G. Pearson (Pearson, 1963) introduced the chemical hardness concept and defined the chemical hardness as the resistance against the electron cloud polarization of atomic and molecular systems (Kaya and Kaya, 2015b). Classifying the Lewis acids and Bases as hard and soft, same scientist introduced Hard and Soft Acid-Base Principle (Pearson, 1963) noting that "Hard acids prefer the binding to hard bases and soft acids prefer the binding to soft bases." It is widely reported that hard chemical species exhibit low polarizability while soft ones have polarizable electron clouds. Interactions in the living body and the toxic or drug effects of various chemicals can be explained through HSAB Principle. According to HSAB Principle, it can be said that a toxic matter interacts with biological structures having similar hardness or softness. For example, one can easily explain considering HSAB Principle why heavy metal ions like $Pb^{2+}$ and $Hg^{2+}$ are toxic for human body. In the hard and soft classification of Pearson, heavy metal ions mentioned are among soft acids. Such soft acids tend to be strongly bonded to a soft base like $S^{2-}$. Methionine and cysteine are amino acids including S atom in their side chains. When the body is exposed to these heavy metal ions, these ions deactivate the protein by binding to amino acid sulfur. Death is inevitable when overexposure to heavy metal ions. LoPachin and Gavin (LoPachin et al., 2012) applied the Hard and Soft Acid-Base Principle to toxicant- target interactions. The irreversible covalent interaction between a toxic electrophile and a nucleophilic target causes to cell injury. In the body, a toxic electrophile interacts strongly with biological systems to which it is similar in chemical hardness. It can be easily understood from this information; HSAB Principle is a useful tool in terms of the highlighting of the nature of the chemical interactions in the body. In cancer research, the chemical reactivity analysis of studied chemical species is quite essential. Sadler and coworkers (Liu et al., 2011) published a paper entitled "Contrasting Reactivity and Cancer Cell Cytotoxicity of Isoelectronic Organometallic Iridium (III) Complexes" giving important information for the relation between anticancer behaviors of chemical system and chemical reactivity. In this review article, the reason of the giving of detailed information about well-known electronic structure principles is to encourage the consideration of the principle mentioned in experimental and theoretical cancer research.

Another electronic structure principle regarding to chemical hardness concept is Maximum Hardness Principle proposed by Pearson (Pearson, 1993; Kaya and Kaya, 2015c). After the introducing of famous Hard and Soft Acid-Base Principle, Pearson reported the Maximum Hardness Principle as "there seems to be a rule of nature that molecules arrange themselves so as to be as hard as possible. It is apparent from this explanation that chemical hardness is a remarkable indicator of the stability. If so, one can say that hard chemical systems exhibit higher stability than soft ones.

Hard chemical species cannot exhibit high polarization. In hard and soft classification of Pearson, there is remarkable linkage between hardness and polarizability (α). The powerful relation between hardness and polarizability concepts has been mathematically proven by Ghanty and Ghosh (Ghanty and Ghosh, 1993). From the results obtained in the paper of these authors, it can be noted that softness is closely related the cube root of the polarizability. Minimum Polarizability Principle has been proposed considering the inverse relation between hardness and polarizability and Maximum Hardness Principle. This important principle imparted to the scientific literature by Chattaraj and Sengupta (Chattaraj and Sengupta, 1996) states that in a stable state, polarizability is minimized unlike the chemical hardness. It is not difficult to predict that polarizability is a useful descriptor like chemical hardness to explain the interactions between chemical species.

Minimum Electrophilicity Principle is among the widely used electronic structure principles. This principle proposing the minimization of electrophilicity index like polarizability in stable states has been published inspired by Maximum Hardness Principle and Parr's electrophilicity index. It should be noted that we should be careful in the using for chemical reactivity analysis of Minimum Electrophilicity Principle because it includes some remarkable limitations. In a recent paper, von Szentpály, Kaya and Karakuş (von Szentpály et al., 2020) investigated the limitations, validity and physical basis of Minimum Electrophilicity Principle. In the same paper presenting new theorems and guiding rules about Minimum Electrophilicity Principle, authors introduced the "Maximum Composite Hardness Rule" proposing that a composite descriptor like $\eta_M/V_m^{1/3}$ ($\eta_M$: molecular hardness and $V_m$: molar volume) can be more useful compared to single descriptors in terms of the chemical reactivity analysis.

*Chemical hardness based applications in lung cancer*

As noted in the previous parts, chemical hardness is one of the important quantum chemical parameters used in the prediction of the chemical reactivities of chemical systems. In the introducing of HSAB Principle, Pearson classified the Lewis acids and bases as hard, soft and bonderline. In Table 3, Classification as hard, bonderline and soft of Lewis acids and bases is presented. It can be seen from this table that heavy metal ions are among the soft acids. It is well-known that almost all heavy metal ions are carcinogens. International Research Agency for Research Cancer reported as group 1 carcinogens the arsenic cadmium chromium and nickel (Smith et al., 1997). Some researchers noted that these chemicals effect in a negative manner the tumor suppressor gene expression, damage repair processes, and enzymatic activities in the body by causing oxidative stress. In these effects, the chemical hardness of the mentioned chemicals plays important role.

Asath and coworkers (Asath et al., 2017) presented a detailed analysis on N, N-di-tert-butoxycarbonyl (Boc)−2-amino pyridine (DBAB) for its considering in the lung cancer treatment. The experimental and theoretical studies made showed that the mentioned molecule has high inhibition effect against the epidermal growth factor receptor (EGFR) protein which is one of the widely reported reasons of lung cancer. In the study, it was proposed that in the development of new drugs for lung cancer treatment, this molecule can be considered. As a result of the analyses in the light of Frontier Orbital Approach, it was noted supporting its stability that the molecule has higher hardness and lower softness values.

In Fig. 5, Molecular Docking results for the interaction with some protein targets considered in lung, skin, brain and gastric cancers of

**Table 3**
Classification as hard, bonderline and soft of Lewis acids and bases (Pearson, 1963).

| Acids | Bases |
|---|---|
| **Hard acids** | **Hard bases** |
| $H^+$, $Li^+$, $Na^+$, $K^+$, $Rb^+$ | $H_2O$, $OH^-$, $F^-$ |
| $Be^{2+}$, $Mg^{2+}$, $Ca^{2+}$, $Sr^{2+}$, $Sn^{2+}$, $Al^{3+}$, $Se^{3+}$, $Ga^{3+}$, $In^{3+}$, $La^{3+}$ $Cr^{3+}$, $Co^{3+}$, $Fe^{3+}$ | $CH_3CO_2^-$, $PO_4^{3-}$, $SO_4^{2-}$ |
| $Si^{4+}$, $Ti^{4+}$, $Zr^{4+}$, $Th^{4+}$, $Pu^{4+}$, $VO_2^+$, $UO_2^+$, $(CH_3)_2Sn^{2+}$, $BF_3$, $BCl_3$, $B(OR)_3$ | $Cl^-$, $CO_3^{2-}$, $ClO_4^-$, $NO_3$ |
| $RPO^+$, $ROPO^+$, $RSO^+$, $ROSO^+$, $SO_3$, $I^{7+}$, $I^{5+}$, $Cl^{7+}$, $R_3C^+$, $RCO^+$, $CO_2$, $NC^+$ | $ROH$, $RO^-$, $R_2O$, $NH_3$, $RNH_2$, $N_2H_4$ |
| **Soft acids** | **Soft bases** |
| $Cu^+$, $Ag^+$, $Au^+$, $Tl^+$, $Hg^+$, $Cs^+$ | $R_2S$, $RSH$, $RS$ |
| $Pd^{2+}$, $Cd^{2+}$, $Pt^{2+}$, $Hg^{2+}$ | $I^-$, $SCN^-$, $S_2O_3^{2-}$ |
| $CH_3Hg^+$, $Tl^{3+}$, $Tl(CH_3)_3$, $RH_3$ | $R_3P$, $R_3As$, $(RO)_3P$ |
| $RS^+$, $RSe^+$, $RTe^+$ | $CN^-$, $RCN$, $CO$ |
| $I^+$, $Br^+$, $HO^+$, $RO^+$ $I_2$, $Br_2$, heavy metal ions | $C_2H_4$, $C_6H_6$, $H^-$, $R^-$ |
| **Bonderline acids** | **Bonderline bases** |
| $Fe^{2+}$, $Co^{2+}$, $Ni^{2+}$, $Cu^{2+}$, $Zn^{2+}$, $Pb^{2+}$ | $C_6H_5NH_2$, $C_5H_5N$, $N_3^-$ |
| $B(CH_3)_3$, $SO_2$, $NO^+$ | $Br^-$, $NO_2^-$, $SO_3^-$, $N_2$ |

DBAP molecule are visually presented. The calculations proved that this molecule binds more powerful with the target protein of lung cancer.

Sony and coworkers (Parmar et al., 2021) synthesized a series of the compounds to investigate their anticancer activity against some like cancer cell lines (lung (A549), prostate (PC3), breast (MCF-7), liver (HepG2), colon (HCT-116), ovarian (SKOV-3), skin (A431), brain (U251) and kidney (786-O)). Among the studied compounds, 3-(4-Methoxy-3-(2-methoxypyridin-4-yl)phenyl)-N-(4-methoxyphenyl) azetidine-1-carbothioamide **(3B)** compound was determined the best candidate for against PC3, U251, A431, and 786-O cancer cell lines. In the study considered Hard and Soft Acid-Base Principle also, the chemical hardness values in gas phase and aqueous phase of compound 3B were reported as 2.053 and 2.228 eV, respectively. Jeyaseelan and Benial (Christopher Jeyaseelan and Milton Franklin Benial, 2021) published a paper including spectral analysis, DFT and docking calculations and cytotoxic behavior of 4-nitro-indole-3-carboxaldehyde with a chemical hardness of 2.05 eV. The theoretical and experimental investigations performed proposed the mentioned molecule as an important candidate for the development of new drugs against lung cancer.

It is widely reported that (RS)-N, N-bis(2-chloroethyl)−1,3,2-oxazaphosphinan-2-amine 2-oxide compound reported as Cyclophosphamide (CYC) is used as anticancer agent against some cancer types such as lymphoma, multiple myeloma, leukemia, and small cell lung cancer. It should be noted that in especially lung cancer treatment, the mentioned compound is widely considered. A recent paper penned by Prasath reported the chemical hardness, softness and electrophilicity values of this molecule as: 3.1155, 0.1604 and 1.8045 eV, respectively (Govindammal and Prasath, 2020). Calculated electrophilicity value supports the biological activity of the compound. HOMO-LUMO energy gap of the mentioned compound is given through Fig. 6.

The reason of the adding of such theoretical part in this review is to propose the using of Conceptual Density Functional Theoretical parameters like polarizability, hardness, electrophilicity and Kaya's composite descriptor in cancer researches. It should be noted that electronic structure principles and guding rules about the mentioned parameters provide important clues and insights about the nature and power of the interactions and reactions with important biological systems of selected molecules. Especially chemical hardness is quite useful to predict electrostatic and covalent nature of the interactions. The validity in many biological interactions of HSAB Principle an undeniable fact (Chattaraj and Maiti, 2003; Ho et al., 1978).

## Conclusion

Flavonoids is one important groups of natural molecules having many superior feature. These natural compounds with high antioxidant property are widely used in cancer research. Utilizing different combined possibilities of therapeutic agents and flavonoids, while simultaneously reducing the dose of chemotherapeutics, providing a reduction in toxicity and targeting multiple signaling pathways, successful cancer therapy is promising. For this purpose, it is very important to fully understand the relationship between the different functional groups in the structures of flavonoids and their effect on the molecular mechanism, and to develop and change the basic structure of flavonoids in order to increase their therapeutic efficacy and is essential for an effective cancer treatment. This would greatly benefit the development of improved
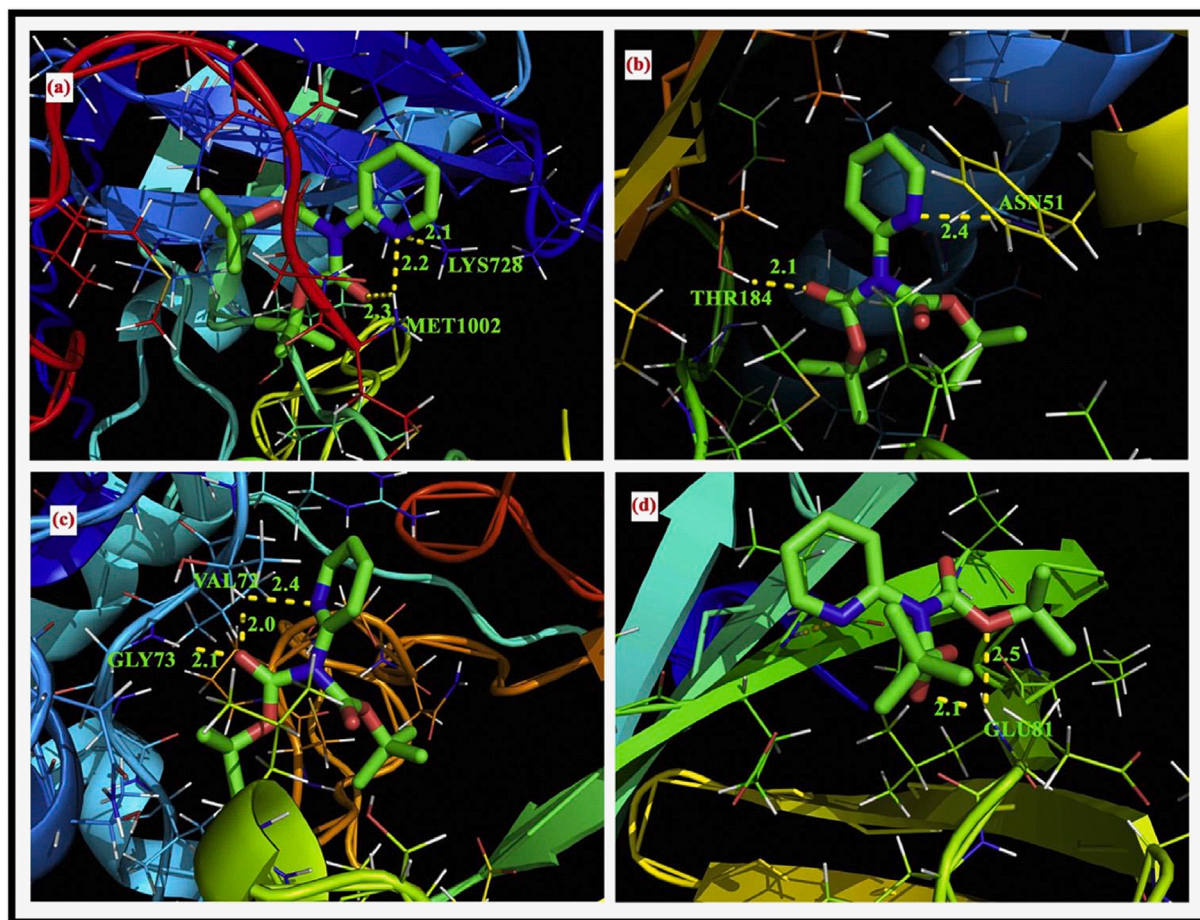


**Fig. 5.** Lowest energy docked poses of the DBAP molecule with various cancer related protein targets such as (a) lung cancer, (b) Skin cancer, (c) brain cancer and (d) gastric cancer (Asath et al., 2017).
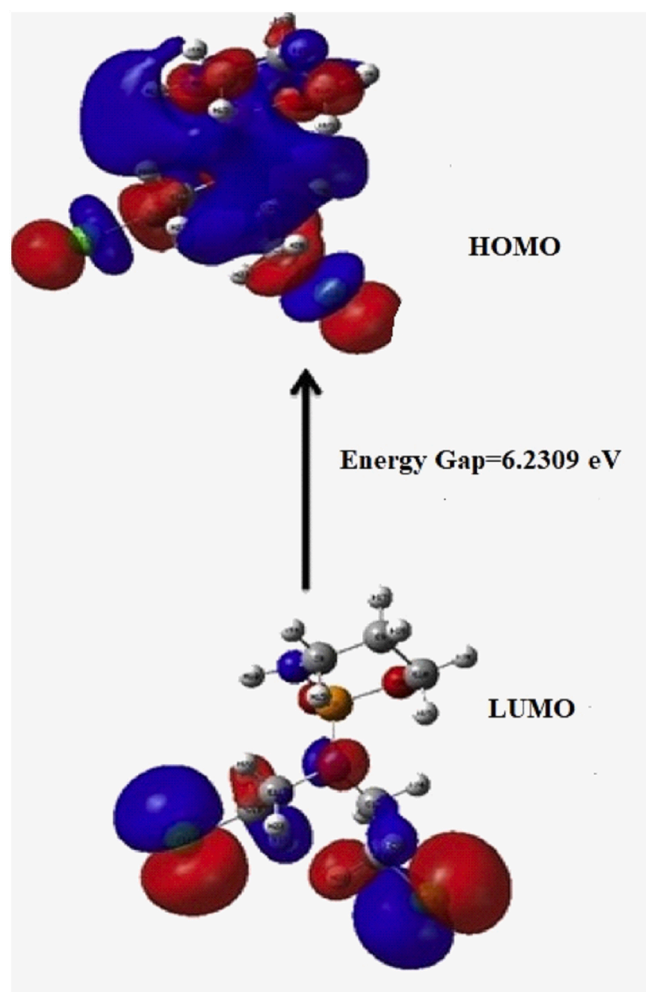
**Fig. 6.** HOMO and LUMO images and energy gap value obtained at B3LYP/ 6–311++*G* (d,p) calculation level of CYC compound (Govindammal and Prasath, 2020).

therapeutic strategies for the prevention and treatment of solid tumors, including lung cancer.

It is clear that revealing the interactions between the functional groups in the structures of flavonoids, fully understanding their effects on the molecular mechanism of cancer, and estimating the structures of flavonoids by enabling the development and modification of them using computer programs containing theoretical approaches will make great contributions to cancer treatments and drug development, including lung cancer. Therefore, this review article will serve as an important resource presenting the relation between flavonoids and their anticancer activities againts lung cancer. In additıon to past and current experimental studies in this topic, we emphasized the usefullness of important electronic structure principles and guding rules like Hard and Soft Acid-Base Principle (HSAB), Maximum Hardness Principle, Minimum Polarizability, Minimum Electrophilicity Principles and Maximum Composite Hardness Rule in the explanation of biochemical interactions and anticancer drug effects of the molecular systems. This review article is more current and comprehensive compared to the other paper published in the paper and it includes new and useful theoretical and experimental strategies on the treatment of lung cancer.

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