REVIEW ARTICLE

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Matricaria Chamomile Protective Effect Against Type-2 Diabetes Mellitus and Cancer Cell Linings

*Shahnai Basharat, [1]Syed Amir Gilani[2] , Faiza Iftikhar [3] , Muhammad Mustafa Qamar[4] , Mian Anjum Murtaza, Sanabil Anmol[6] , Amna Imtiaz[7], Sammana Ghazanfer[8], Ameer Hamza[9], Affifa Rajpoot[10]

Corresponding Author:
Shahnai Basharat
E-mail: shahnaibhatti@gmail.com
Assistant Professor, University Institute of Diet & Nutritional Sciences the University of Lahore

Abstract

Matricaria Chamomile is one of the most famous herbal medicines in ancient times, which is known as mankind. This plant is belonging to the Asteraceae family. It is named by two very well-known species, German and Roman kind. Extracts of chamomile plant and dried flower consist of many terpenoids and flavonoids including luteolin as well as apigenin. These flavonoids and terpenoids play a vital role in protecting against chronic diseases such as Type-2 Diabetes Mellitus and Breast Cancer. Recent reports of 2015 have shown that prevalence of these two diseases has increased death rate globally as well as in Pakistan. Chamomile tea and other extracts containing its bioactive components (luteolin and apigenin) are used in many experimental studies for investigating their effect against diabetes and cancer cells. This review on inhibitory effects of chamomile plant in diabetes and cancer includes many latest types of research, in which studies investigated human cells and rat cells. Subjects in the form of groups or individuals were given chamomile extracts to observe the effect on glycemic index in diabetes and induced apoptosis of cancer cells. It was viewed that chamomile extracts showed remarkable effect on glycemic index and induced apoptosis to inhibit cancer cell growth. These all studies were conducted in past 4 years and have detailed beneficial effects of chamomile as herbal medicine. In this review chamomile's origin, nutritional content, herbal properties and latest researches over inhibitory effects on diabetes and cancer cell growth are being highlighted.

Keywords: Matricaria Chamomile, Anti-Diabetic, Anti-Cancer, Luteolin, Apigenin, Apoptosis

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INTRODUCTION:

Herbal Medicine an Ancient Gem

According to an estimate, there are three-fifty hundred thousand to approximately four hundred thousand varieties of plants present in the world (1). In which large number of plant varieties are used in treatment and prevention of different health concerns, World Health Organization (WHO) has proposed that eighty percent of human population throughout the world depends and uses herbal medications for use in case of any health issue (2). More than 90% of medicinal products in the modern era and health care frameworks were from plant sources and most cases were propelled by their utilization from antiquated. Distributed reports are depicting the exchange of restorative and sweet-smelling plants as an administration with worldwide

esteem of sixty billion US$(3). This esteem is relied upon to considerably exhaust to a bigger Degree constantly by 2050 because of the expanding pattern and notoriety of homegrown medications. Over the Most recent couple of years in Pakistan, critical logical and business patterns have been seen due to the far-reaching social agreeableness and monetary capability of plants'-based items (4). The country populace depends more on assortment of conventional homegrown cures because of the need for access to present-day pharmacopeia. (5)

Chamomile; Origin, Uses, and Nutritional Value

Chamomile is the ancient and broadly used medicinal plant (6). It belongs to the daisy family and represented by two most known varieties Roman chamomile which is considered as a common species (7) and Matricaria Chamomile which is known as wild chamomile. Both varieties are used in the making of medicine and herbalism (6). Matricaria chamomile is the popular source of chamomile and has been used since ancient times for medicinal purposes. Many products including food, beverages, and cosmetics as insects and pest control in veterinary medicine contain extract and flowerets of chamomile. (8) In many biological activities, chamomile extracts and their essential oils have been involved. (9) which shows many health benefits, for example, anti-diabetic, anti-cancer, anti-inflammatory, antimicrobial, antiseptic, immune-modulatory and helps in wound healing. (10) Matricaria chamomile a very famous type of chamomile is used in different medical problem especially as an herbal product (6).

In chamomile, 120 components have been recognized, containing thirty-six flavonoids, twenty-eight terpenoids and also fifty-two supplementary compounds showing potential pharmacological properties. (11) The chamomile plant is rich in phenolic compounds (12) responsible for its antioxidant activity. These dominant phenolic and flavonoid compounds consist of umbelliferone, chlorogenic acid, luteolin, apigenin, quercetin, and naringenin (13)

Mechanism

Researches have confirmed by performing experiments that chamomile-extracts has anti-diabetic and anti-cancer actions. (14) It's aqueous-compounds decreased the amount of glucose in the blood and free-radical formation among people suffering from diabetes, (15) who were also given streptozotocin (16) Modern researches showed that this plant has substances that are phytochemical-polyphenolic in nature. These compounds lead to pro-oxidation outcomes when studied in glass tube. Phenoxyl-radicals lead to the possible disintegration of membrane of the mitochondria among broader group of cancerous cells. (16)

Prevalence Rate of Diseases:

In Pakistan, 95% of women are suffering from breast cancer. The proportion of female to male was 100:2, the majority of cases belonged to Lahore. Gastric cancer is the second most frequent source of death (18) amidst all types of cancer. Its death rate in Pakistan is 6541 fatalities annually (19). Data from the year 2015 report, that Pakistan has more than seven million diabetic patients. (20) The worrying bit about is that this prevalence rate is said to double in the next 20 years (21).

Rationale of the Article

According to previous studies, there is a strong relationship between chamomile tea and disease management such as diabetes, cancer, anxiety, depression, natural allergy fighter, anti-inflammatory, muscle spasm, menstrual disorders, ulcers, and gestational diseases. Chamomile tea or oil manufacturing is used to treat many human problems including allergic rhinitis, infections due to free radicals, muscle cramps, disorders of menstruation, sleep deprivation, internal injuries, wounds, GIT disorders, rheumatic arthritis. Essential oils of chamomile are used broadly for production of beauty products and in aromatic therapies. Much different processing related to chamomile has been produced. The most commonly used is in the form of herbal tea and its intake is greater than 1 million cups in a day. Therefore, the aim of this review article was to explore the evidence and mechanism of chamomile in the management of inflammatory and chronic disease.

Review of literature:

Chamomile Recutita-L has been used as herbal medicine because of their many health uses which involve anti-inflammatory, anticancer, antispasmodic, radical-scavenging effects and others (22) Luteolin is a bioactive flavonoid found in abundant form in chamomilla (23) which has justified its inhibitory effects in inflammation, cancers, and diabetes. Past investigations have revealed that an agent which has properties against inflammation and oxidation is Luteolin.

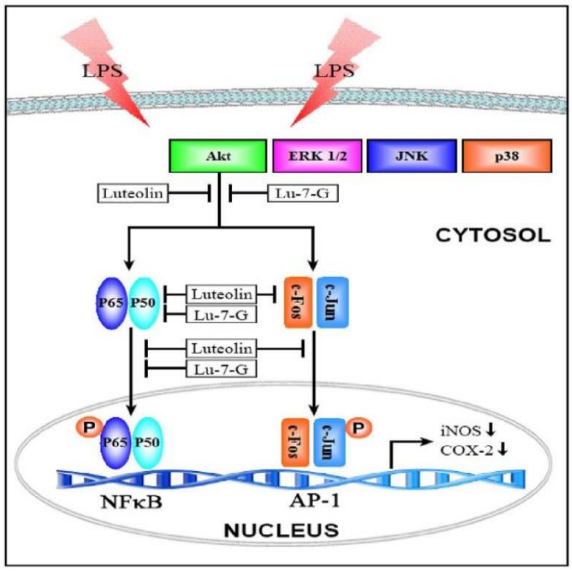

Fig.1. The effects of luteolin against inflammation

According to Fig.1. The investigation, the ability of luteolin against inflammation (24) and its one glycosidic forms, luteolin-7-O-glucoside, was being analyzed comparatively and their working operations were studied on molecular level. Inactivated RAW 264.7 cells of Lipo-poly-saccharide (LPS) chamomile vital flavonoid component luteolin has more effectively hindered the inflammatory effect of oxygen species including nitric oxide (NO) and prostaglandin E2. On the other hand, also inhibited the formulation of their enzymes produced parallel including cyclooxygenase-2 and inducible NO synthase (iNOs) comparative to luteolin-7-O-glucoside. These mechanisms were done at molecular level for investigating, either the inflammatory responses were related to the sequence-specific DNA binding factor, nuclear factor (NF) and activator protein (AP)-1 or these were only formed as a by-products from signaling molecules, mitogen-activated protein kinases (MAPKs) and phosphoinositide 3-kinase (PI3K) (25) The chamomile flavonoid luteolin demolished the charge of both sequence-specific DNA binding factors including nuclear factor as well as activator protein, but on the other hand, luteolin-7-O-glucoside only inhibited the processing effect of Nuclear factor. However, both of the flavonoids luteolin and luteolin-7-O-glucoside hindered the process of protein kinase B phosphorylation in an exposure-response way (26) Hence, luteolin effectively enhanced inflammation induced by LPS as compared to luteolin-7-O-glucoside, which may be covering the differentially activated nuclear factor, Activator protein-1, PI3K-Akt pathway in RAW cells (27).

Anti-diabetic effect of chamomile tea:

High blood glucose levels can be lowered by using chamomile which has been reported in many studies. Blood sugar and HbA1c levels of rats with diabetes were studied and samples were taken before and after meal intake. As a result, glucose was lowered due to chamomile tea consumption. Obesity rates were also reduced in diabetic rats due to chamomile. (28) Chamomile has a strong anti-diabetic role that is why it should be consumed daily for better results (6). Diabetes induced by Streptozotocin in rats was also controlled by using chamomile extract (29) and its active components. Fasting blood glucose level in streptozotocin induced diabetic rats was lowered by chamomile leaves extract.

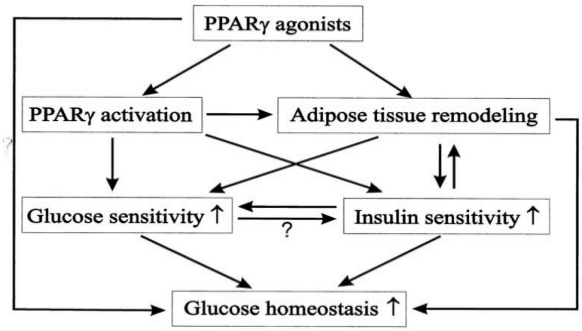

Fig.2. A cycle of chamomile tea affects the sensitivity of insulin by peroxisome proliferator-activated receptor

Chamomile tea affects the sensitivity of insulin by peroxisome proliferator-activated receptors. The cycle of its regulation (Fig.2.) has important role in fats and sugar balance. Insulin sensitivity and abnormal amount of lipids in blood can be lowered by changing PPARs route. Peroxisome proliferator-activated receptors are further split into three different kinds. These are alpha, beta, and gamma. PPARs gamma is associated with insulin sensitivity and sugar metabolism in hyperglycemic patients. PPARs are triggered by some enzymes, especially in fat cells. The bioactive compound of chamomile is luteolin. (30) Luteolin is responsible for increasing the sensitivity of insulin and transcriptional activation of peroxisome proliferator gamma-activated receptors. Glucose can be stored in muscles and peripherals by adenosine monophosphate-activated protein kinase enzyme and PPARγ gene expression. The expression of the gene is also enhanced by luteolin. In addition, gluconeogenesis restriction inhibits glucose formation due to adiponectin (16).

Mechanism of chamomile effect on diabetes treatment:

The proposed mechanism for the anti-diabetic effect of chamomile extract is due to activation of PPARs. Fig.3. shows that chamomile molecules bind to the receptor sites of PPARs and activate them. PPARy increases insulin sensitivity in fat tissues by the regulation of adiponectin. Glucose is stored in adipocytes and gluconeogenesis is also inhibited. In this glucose homeostasis is achieved in diabetic patients by administration of chamomile (31).

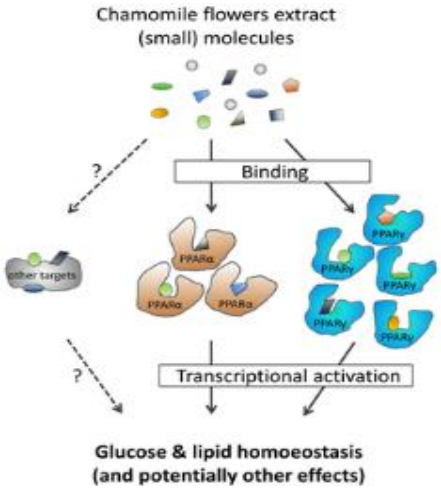

Fig.3. Mechanism of chamomile effect on diabetes treatment

Evidence-based experimental studies:

A study was conducted on 50 diabetic patients between the ages of 30-70 years. The sample of this study was divided into two groups (1) Experimental group and (2) Control group. The experimental group received standard treatment with orally 200 ml/day of chamomile infusion according to 10 g/100 mL boiling water two times in a day, before lunch and dinner for 28 days. Moreover, the control group received standard therapy. The result of this study indicated that, due to chamomile intake, there was significant control in blood sugar levels. By comparing these two groups, there was a significant decrease in fasting blood sugar and 2h postprandial glucose in test group was also reduced. Furthermore, chamomile has potential desirable effects on serum levels of TC, LDL-C, and Cr in patients with type 2 diabetes taking oral hypoglycemic agents. (32)

Another similar study was being done to access anti-glycation effect of mixed herbal extract in the individual with pre-diabetes Mellitus. Hot water extraction from Anthemis nobilis (Roman chamomile) and Vitis vinifera (grape leaf) was used to make mix herbal extract. A group of 26 volunteers including 21 males and 5 females age 8-55 years were taken for this study. All these group members suffered from pre-diabetes Mellitus. Moreover, the group members were further divided into two subgroups (a) Test group (b) Control group. The test group contains 13 participants aged 8-52 years as well as control group having 12 participants age 8-50 years. For eight weeks, 1200 mg of mixed herbal extract was administrated to the test group. The result of this study indicated that mixed herbal extract retards the mechanism of abnormal sugar and also improves the symptoms which are related to the quality of life. Furthermore, 8 weeks mixed herbal extract supplementation have significant impact on reducing the risk of diabetes. (33)

Oxidative Stress is a major contributing factor in the pathogenesis of problems occurring in diabetes. A study was undertaken to analyze the impact of chamomile tea intake on patients who suffered in oxidative stress with type-2 diabetes mellitus. 64 participants including males and females with type-2 diabetes mellitus between the ages of 30-60 years selected for this study. For eight weeks, half of the group participants were initiated with chamomile tea which was three grams per one fifty mL heated water, immediately after the meals. Remaining half participants were control groups following a water regimen for same intervention time period. At start and finish of the experiment, blood samples in fasting condition, height-weight measurements and dietary history including 24-hour recall since three days were taken. The result of this study showed that tea of chamomile extracts significantly reduced the concentration of glycosylated hemoglobin, insulin levels in serum and model of homeostatic assessment for resistance of insulin in participants of intervention group as compared with control group. Chamomile tea has a great effect on reducing the glycemic level of diabetic patients (type-2). (16)

Chamomile and its products play a very beneficial role in the reduction of problems related to depression and diabetes. A study was conducted on chamomile to analyze its impact on blood sugar levels and depression in type 2 diabetes. In this study, 74 participants having type-2 diabetes mellitus were selected. Participants were divided randomly into two groups named as chamomile tea group and black tea group. Each group consists of 37 members. Chamomile tea group received 3 cups of chamomile tea daily while black tea group received 3 cups of black tea daily. The tea was served to both groups after half-hour of meal for 12 weeks. Blood lipid profiles and hemoglobin test for diabetes was being done after intervening. After the comparison of these two groups, the result of the study designated that,

drinking three cups of chamomile tea daily for 12 weeks for those who are suffering from type-2 diabetes leads to improve blood sugar levels. Therefore, people with type-2 diabetes mellitus are recommended to drink chamomile tea. (34)

Another study has been done to analyze the impact of chamomile Recutita flowers to check the hypoglycemic and hepatorenal levels in streptozotocin-diabetic rats. Five groups of albino rats were taken for the experiment. The extract of 500 mg kg-1 was given to the desired group and observed for 4 weeks on daily basis. Serum marker enzymes and kidney functions were also examined. Lipid peroxidation and activities of glutathione peroxidase were evaluated to check the oxidative stress. By reviewing the extracts decrease in the glucose level and increase in Glutathione peroxidase were observed. In diabetic rats, other liver enzyme activities like AST, ALT, ALP, urea, and creatinine were also noted to be decreased. So, the study result showed that the flower chamomile Recutita has a protective effect against hypoglycemic, hepatorenal levels in the diabetic rats. (35)

Table 01: Evidence from Experimental Studies and their effects

Sr.no	Dietary Compound & Dosage	Subject	Duration	Effect/Results
1.	Chamomile infusion 200ml/day (2 times/day)	50 Diabetic patients 30-70yrs	4 weeks	Lowering Blood Sugar level
2.	Mixed Herbal extract (Anthemis nobilis + Vitis vinifera)	26 Diabetic volunteers 8-55 yrs.	8 weeks	Lowering Risk of Diabetes
3.	Chamomile tea 3g/150mL	64 Diabetic Individuals 30-60yrs	8 weeks	Lowering Glycemic level of DM type-2
4.	Chamomile tea 3cups/day	74 patients	12 weeks	Improved Blood sugar level in DM
5.	Chamomile flower 500mg/kg	5 groups of Albino rats	4 weeks	Protective effect against hyperglycemia

Chamomile Effect on Cancer

Chamomile revealed to contain anti-cancerous properties. These properties are the result of flavonoids apigenin and luteolin present in chamomile. Luteolin a hydroxylated flavone derivative rich in chamomile demonstrated its inhibitory activity against cancer cell proliferation. Results of various studies showed that luteolin inhibits cancer cell growth through multiple mechanisms. These mechanisms followed by cell cycle arrest and apoptotic activity. Down-regulation mechanism is one of the basic mechanisms showed by luteolin in breast cancer. In mice, luteolin tends to decrease cancer activity at significant level. In conclusion, the breast tumor growth successfully suppressed by the flavonoid luteolin present in chamomile hence advised as a potential inhibiting agent in breast tumor growth in studies as well as its anticancer activity may be explained by their inhibitory actions on EGFR pathway. (36)

Evidence-based experimental studies

Apigenin and luteolin are two active flavonoids present in chamomile that are proven to have performed the anti-cancer activity. In a 2018 study both of these flavonoids were tested in a 3-dimensional analysis against breast cancer spheroids through lymph endothelial cells. Both flavonoids subdued trigger factors in breast cancer cells. Concentrations of luteolin and apigenin were tested along with cultured breast cancer cells. A single 60mg/kg oral dose of apigenin and a single 14.3mg/kg dose of luteolin given to rats achieved peak plasma concentrations. Both flavonoids inhibited mechanisms at the tested concentrations by working against various cancer cell pathways and gene expressions. (37)

Cholangiocarcinoma in human cells can be controlled by using luteolin, an important component of chamomile. Cell division, the progression of cell cycle can be prevented by luteolin in abnormal cells. A signaling pathway that induces cancer is also

Table 02: Evidence based experimental studies

Sr.no.	Dietary Compound & Dosage	Subject	Duration	Effect/Result
1.	Apigenin(60mg/kg) Luteolin(14.3mg/kg)	Rats	N/A	Suppressing effect on Breast cancer cells
2.	Sulfo-rhodamine (100 uM)	Human cells	24h or 48 h	Induced apoptosis in cancer cells
3.	5-fluorouracil 20 mg in two parts	25 patients	One for 3 weeks One for 5 weeks	Inhibited cancer growth
4.	Chamomile extract Multiple dosage(2600, 1300, 650)mg/mL	Female breast cancer cells	24 hr.	Inhibited cancer growth Increased protein caspase-3 level
5.	Hydrochloric extract of chamomile (multiple dosages)	MCF-7 MDA-MB-468 Cell lines of breast cancer	24hr/48hr/72hr	Antitoxic Anti-migrative Anti-invasive
6.	10mM solution of apigenin	Human colorectal cancer cells	N/A	Activating Wnt signaling pathway

blocked by luteolin. The sulfo-rhodamine assay was used to examine the effect of luteolin in cells against cancer of bile duct. Abnormal cells were treated with various concentrations of luteolin as 1, 5, 10, 25, 50 and 100 μM for 24 or 48 h. Cell growth was strongly inhibited after 24 and 48 h of treatment with luteolin. The results showed that 10 μM luteolin slightly induced apoptosis in cells. Treatment with 50 μM luteolin, however, remarkably induced apoptosis in carcinogenic cells. It also suppresses phosphorylation and helps in control of cancer. (38)

Apigenin found in chamomile enhances anticancer activity and it is used in treatment of hepatocellular carcinoma. In this study, effect of apigenin on intensifying the chemosensitivity of HCC cells in response to 5-fluorouracil in 25 patients was studied. The concentration of apigenin sufficiently enhances to cytotoxicity of 5-FU in HCC cells. Combined treatment 20mg five times 3 weeks and 5-FU 20mg for 5 days significantly inhibited the growth of hepatocellular carcinomas tumors in humans under observation. This study explains that apigenin may potentiate the cytotoxicity of 5-FU in HCC via inhibition of reactive oxygen species-mediated drug resistance and activation of mitochondrial pathways of apoptosis. (39)

The study was conducted to investigate the effect of chamomile on breast cancer cells. T-47D and 4T1 in comparison with the control group. The activation of apoptotic pathways and the level of caspase3 protein (Mediators of program cell death) in breast cancer cells were also have been examined to identify the mechanism of action through which chamomile inhibits cancer activity. The breast cancer cells were treated with aqueous extract of chamomile at different concentrations 2600, 1300, 650 and 325 micrograms per milliliter. After 24 hours the level of caspase3 protein, cytotoxic activity, and apoptotic activity were examined. Resulting in the significant reduction of breast cancer cells and increase in caspase3 protein in females, signifying the activation of apoptosis in breast cancer cells. In conclusion, the extract of chamomile induces apoptosis to inhibit cancer cell growth by increasing the protein level of caspase3 in breast cancer. (40)

In 2017 the study was conducted on MCF-7 and MDA-MB-468 cell lines of breast cancer in order to investigate the anti-proliferative and antitoxic activity of chamomile in the dose and time-dependent manner. The cells were treated with different concentrations of hydroalcoholic extract of chamomile for 24h, 48h, and 72 h. This study expressed the 50% growth inhibition concentrations, 30.2% apoptosis and 17.3% necrosis at concentrations of 1000 μg/mL. After 24, 48, and 72 h of treatment reduction in cellular proliferation or migration, number of clone formation, invasion, and attachment were seen in MCF-7 and MDA-MB-468 cell lines, compared with control group. The result shows the antitoxic, anti-migrative and anti-invasive properties of chamomile on breast cancer in time and dose-dependent manner. (41)

A study carried out in 2016 aimed to investigate the effect of apigenin on the invasion and also the migration of colorectal cancer cells as well as the Wnt signaling pathway that is important to search for potential drugs that might be anti-cancerous. A

10mM solution of apigenin, as well as human colorectal cancer cell lines, were used in the experiments. Results revealed that apigenin unquestionably restrained not only the proliferation but also the invasion, migration and organoid expansion of colorectal cancer cells. It performed this inhibitory action by restraining the Wnt signaling pathway that regulates cancer cells (42).

CONCLUSION

The present review has been done to focus on the protective effect of herbs on the management of diabetes mellitus and cancer. The documentation, monitoring, and reporting of experiment-based data is a critical baseline step in proper prescribing and adequate counseling for patients. In general, Apigenin and other bioactive components have played a vital role in making chamomile a magical herbal drug. Further, both long- and short-term experimental studies are required to fully understand the health benefits of chamomile herb in prevention and treatment of different health complications, and it should be adopted in the field of nutrition and medicinal sciences.

References

1. Chandler, S. F. and C. Sanchez (2012). Genetic modification; the development of transgenic ornamental plant varieties. Plant biotechnology journal 10(8): 891-903.

2. Folashade, O. (2012). Standardization of herbal medicines-A review. International Journal of Biodiversity and Conservation 4(3): 101-112.

3. Hamilton, A. (2013). Plant conservation: an ecosystem approach, Routledge.

4. Sher, H. (2015). Indigenous knowledge of folk medicines among tribal minorities in Khyber Pakhtunkhwa, northwestern Pakistan. Journal of ethnopharmacology 166: 157-167.

5. Egharevba, H. O. (2015). Integrating traditional medicine practice into the formal health care delivery system in the new millennium–the Nigerian approach: a review. Int J Life Sci 4(2): 120-128.

6. Khan, S. S. (2014). Chamomile tea: Herbal hypoglycemic alternative for conventional medicine. Pakistan journal of pharmaceutical sciences 27.

7. Guimarães, R. (2013). Nutrients, phytochemicals and bioactivity of wild Roman chamomile: a comparison between the herb and its preparations. Food Chemistry 136(2): 718-725.

8. Khater, H. F. (2012). Prospects of botanical biopesticides in insect pest management. Pharmacologia 3(12): 641-656.

9. Roby, M. H. H. (2013). Antioxidant and antimicrobial activities of essential oil and extracts of fennel (Foeniculum vulgare L.) and chamomile (Matricaria chamomilla L.). Industrial crops and products 44: 437-445.

10. Fahad T, Shameem I. (2018). An evidence based approach to the management of cervical cancer in unani system of medicine: A. Journal of Pharmacognosy and Phytochemistry. 7(2):2536-44.

11. Shojaii, A. and M. Abdollahi Fard (2012). Review of pharmacological properties and chemical constituents of Pimpinella anisum. ISRN pharmaceutics 2012.

12. Savoia, D. (2012). Plant-derived antimicrobial compounds: alternatives to antibiotics. Future microbiology 7(8): 979-990.

13. Formisano, C. (2015). Correlation among environmental factors, chemical composition and antioxidative properties of essential oil and extracts of chamomile (Matricaria chamomilla L.) collected in Molise (South-central Italy). Industrial crops and products 63: 256-263.

14. Matić, I. Z. (2013). Chamomile and marigold tea: Chemical characterization and evaluation of anticancer activity. Phytotherapy research 27(6): 852-858.

15. Emam, M. A. (2012). Comparative evaluation of antidiabetic activity of Rosmarinus officinalis L. and Chamomile recutita in streptozotocin induced diabetic rats. Agric. Biol. JN Am 3(6): 247-252.

16. Rafraf, M. (2015). Effectiveness of chamomile tea on glycemic control and serum lipid profile in patients with type 2 diabetes. Journal of endocrinological investigation 38(2): 163-170.

17. DeSantis, C. (2014). Breast cancer statistics, 2013. CA: a cancer journal for clinicians 64(1): 52-62.

18. Ferlay, J. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer 136(5): E359-E386.

19. Daniyal, M. (2015). Risk factors and epidemiology of gastric cancer in Pakistan. Asian Pac J Cancer Prev 16: 4821-4824.

20. Chen, L. (2012). The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature reviews endocrinology 8(4): 228.

21. Atiq, M. A. (2018). Epidemiology Of Non-Communicable Diseases In Pakistan: Are We On The Right Track? The Pakistan Journal of Medicine and Dentistry 6(4): 52-56.

22. Biglar, M. (2012). A preliminary investigation of the jack-bean urease inhibition by randomly selected traditionally used herbal medicine. Iranian journal of pharmaceutical research: IJPR 11(3): 831.

23. Ramešová, Š. (2013). The oxidation of luteolin, the natural flavonoid dye. Electrochimica Acta 110: 646-654.

24. Nabavi, S. F. (2015). Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. Brain research bulletin 119: 1-11.

25. Xia, F. (2014). Luteolin protects HUVECs from TNF-α-induced oxidative stress and inflammation via its effects on the Nox4/ROS-NF-κB and MAPK pathways. Journal of atherosclerosis and thrombosis: 23697.

26. Liu, Y. (2014). Luteolin protects against high fat diet-induced cognitive deficits in obesity mice. Behavioural brain research 267: 178-188.

27. Park, C. M. and Y.-S. Song (2013). Luteolin and luteolin-7-O-glucoside inhibit lipopolysaccharide-induced inflammatory responses through modulation of NF-κB/AP-1/PI3K-Akt signaling cascades in RAW 264.7 cells. Nutrition Research and Practice 7(6): 423-429.

28. Sebai, H. (2014). Antidiarrheal and antioxidant activities of chamomile (Matricaria recutita L.) decoction extract in rats. Journal of ethnopharmacology 152(2): 327-332.

29. Babu, P. V. A. (2013). Recent advances in understanding the anti-diabetic actions of dietary flavonoids. The Journal of nutritional biochemistry 24(11): 1777-1789.

30. Caleja, C. (2015). Development of a functional dairy food: Exploring bioactive and preservation effects of chamomile (Matricaria recutita L.). Journal of functional foods 16: 114-124.

31. Weidner, C. (2013). Antidiabetic effects of chamomile flowers extract in obese mice through transcriptional stimulation of nutrient sensors of the peroxisome proliferator-activated receptor (PPAR) family. PloS one 8(11): e80335.

32. Kaseb, F. (2018). The effect of chamomile (Matricaria recutita L.) infusion on blood glucose, lipid profile and kidney function in Type 2 diabetic patients: a randomized clinical trial. Progress in Nutrition 20(1-S): 110-118.

33. Yonei, Y. (2010). Anti-Glycation Effect of Mixed Herbal Extract in Individuals with Pre-Diabetes Mellitus. Anti-Aging Medicine 7(5): 26-35.

34. Kermanian, S. (2018). The Effect of Chamomile Tea versus Black Tea on Glycemic Control and Blood Lipid Profiles in Depressed Patients with Type 2 Diabetes: A Randomized Clinical Trial. Journal of Nutrition and Food Security 3(3): 157-166.

35. ETHANOLIC, C. R. F. (2014). Hypoglycemic, hepato-renal and antioxidant potential effects of Chamomile recutita flowers ethanolic extract in streptozotocin-diabetic rats. american Journal of Pharmacology and Toxicology 9(1): 1-12.

36. Lee, E.-J. (2012). Luteolin exerts anti-tumor activity through the suppression of epidermal growth factor receptor-mediated pathway in MDA-MB-231 ER-negative breast cancer cells. Food and chemical toxicology 50(11): 4136-4143.

37. Hong, J. (2018). Apigenin and luteolin attenuate the breaching of MDA-MB231 breast cancer spheroids through the lymph endothelial barrier in vitro. Frontiers in pharmacology 9: 220.

38. Aneknan, P. (2014). Luteolin arrests cell cycling, induces apoptosis and inhibits the JAK/STAT3 pathway in human cholangiocarcinoma cells. Asian Pac J Cancer Prev 15(12): 5071-5076.

39. Hu, X. Y. (2015). 5-Fluorouracil combined with apigenin enhances anticancer activity through mitochondrial membrane potential (ΔΨm)-mediated apoptosis in hepatocellular carcinoma. Clinical and Experimental Pharmacology and Physiology 42(2): 146-153.

40. Ghaleghazi, F.M., Safari, F., Baharifar, N., Sheikhi, A. (2018). Investigating the cytotoxic effect of chamomile aqueous extract on 4T1 and 47D cells and level of caspase3 protein in breast cancer cells T-47D. Middle East Journal of Family Medicine.7 (10):62.
41. Nikseresht, M., Kamali, A.M., Rahimi, H.R., Delaviz, H., Toori, M.A., Kashani, I.R., Mahmoudi, R. (2017). The hydroalcoholic extract of Matricaria chamomilla suppresses migration and invasion of human breast cancer MDA-MB-468 and MCF-7 cell lines. Pharmacognosy research. 9(1):87.
42. Xu, M., Wang, S., Song, Y.U., Yao, J., Huang, K., Zhu, X. (2016). Apigenin suppresses colorectal cancer cell proliferation, migration and invasion via inhibition of the Wnt/β-catenin signaling pathway. Oncology letters 11(5):3075-80.