IJBPAS, April, 2025, 14(4): 2279-2292

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

THE ROLE OF QUERCETIN AS NEPHROPROTECTIVE AGENT

UDAY A[1], NEMA RK[1], SHARMA H[2], SAHU GK[2] AND KASHYAP S[1*]

1: Rungta Institute of Pharmaceutical Sciences, Bhilai C.G., India

2: Rungta Institute of Pharmaceutical Sciences & Research, Bhilai, C.G., India

***Corresponding Author: Ms. Seema Kashyap: E Mail: kashyapseema85@gmail.com**

Received 15th Dec. 2023; Revised 20th Jan. 2024; Accepted 1st July 2024; Available online 1st April 2025

https://doi.org/10.31032/IJBPAS/2025/14.4.8933

ABSTRACT

Diabetes mellitus (DM) is a group of heterogeneous metabolic conditions in which there are high blood sugar situations (hyperglycaemia) over a prolonged period due to disfigurement in insulin conformation, stashing, and action. DM is also known as Metabolic syndrome, syndrome X or Insulin resistance syndrome. Traditional Medicines deduced from medicinal shops are used by about 70% of the world's population. This review focuses on Indian Herbal medicines used and give a list of medicinal herbs and spices used in Ayurveda as antidiabetic agents and also of retailed medications for prevention of diabetes mellitus, especially in India. Some of herbal medicines with proven antidiabetic and affiliated salutary goods used in treatment of diabetes are as follows- *Dioscorea opposite, Gymnema sylvestre, Momordica charantia, Syzygium cumini, Azadirachta Indica, Pterocarpus marsupium, Asparagus racemosus, Boerhavia diffusa, Tinospora cardifolia, Swertia chirata, Phyllanthus amarus. Berberis aristata, Aloe vera, Commiphora wightii, shilajeet, Piper nigrum, Ocimum sanctum, Curcumalonga*.

Keywords: Diabetes mellitus, Syndrome X, antidiabetic and Ayurveda

INTRODUCTION

Diabetes is a metabolic disfigurement. Which is characterized by hyperglycaemia, (dieting tube glucose ≥ 126 mg/ dl and/ or ≥ 200 mg/ dl 2 hours after 75 g oral glucose), glycosuria, hyperlipidaemia, negative nitrogen balance and occasionally ketonaemia. A wide pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular accumulation acting in vascular difficulties

like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and supplemental. It's a state of inaptly regulated homeostasis of carbohydrate and lipid metabolism, It's one of the major health challenges in recent occasion **[1]**.

Types of Diabetes-

TYPE 1 DIABETES MELLITUS (10% cases) ➢ They're preliminarily called as Insulin dependent diabetes mellitus (IDDM) or juvenile- onset diabetes. They're further classified as **[2], [3]**-

- ➢ Type IA Diabetes mellitus Immune-intermediated diabetes mellitus
- ➢ Type IB Diabetes mellitus: Idiopathic diabetes mellitus

TYPE 2 DIABETES MELLITUS (80% cases)

- ➢ Earlier called non-insulin-dependent (NIDDM) or maturity-onset diabetes

GESTATIONAL DIABETES MELLITUS (4% cases) OTHER SPECIFIC TYPES OF DIABETES (6-10% cases)

TYPE 1 DIABETES:-

Earlier called Insulin-dependent (IDDM), or juvenile-onset diabetes (JOD). This Account for 10% cases usually occurs in non-obese person before the age of 30 Years. They are absolute requirement of insulin replacement as a treatment. Because of lake of both insulin release phase or Beta-cells fails to respond to normal stimuli for insulin release. As per new classification, neither age nor insulin dependence are considered as absolute criteria. So further Type I Diabetes is can be classified into two subtypes **[1, 3, 4, 5]**

A. Type IA and B. Type IB

A. Type IA (Immune Mediate) Diabetes Mellitus:

This type is characterized by Autoimmune Destruction of Beta-Cells which may leads to Insulin deficiency (Reduction in Insulin Production).

B. Type IB (Idiopathic Mediated) Diabetes Mellitus

This type is characterized by insulin deficiency with tendency to develop ketosis but these patients are negative for autoimmune markers.

TYPE 2 DIABETES:-

Earlier called non-Insulin-dependent (NIDDM), or maturity-onset diabetes (MOD). This account for 80% cases usually which is occurs in older individuals and obese adolescent children. Many Type II Diabetes patients require Insulin to prevent hyperglycemia, and ketosis and thus are not truly non-insulin dependent. The basic metabolic defect in type II Diabetes is either impaired insulin secretion and or insulin **[6, 7]**.

Graph 1: The ratio between cases of diabetes in India and worldwide **[8, 9]**:-

Graph 2: The ratio between cases of diabetes in both gender:-

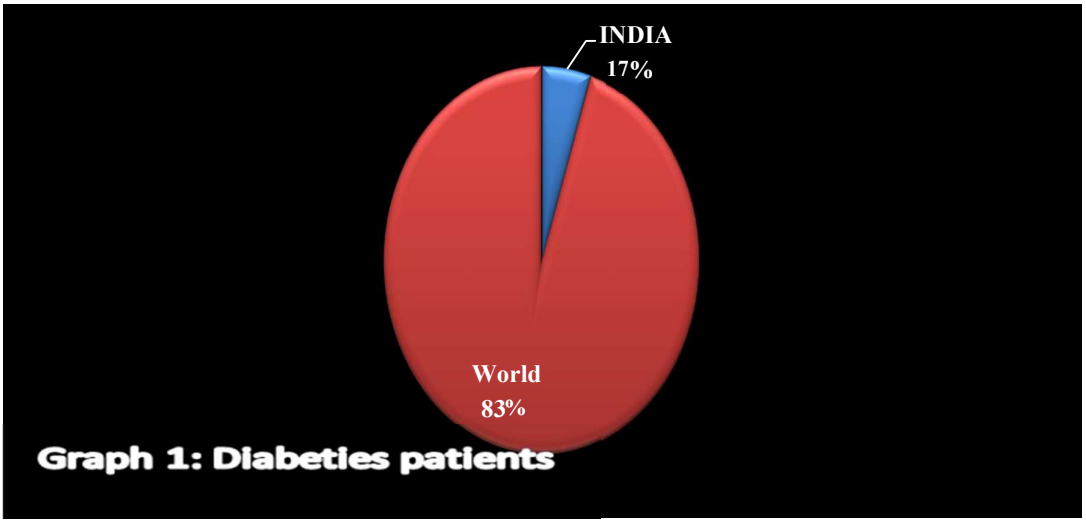

Figure 1: Graph shows diabetes patients ratio in India & World

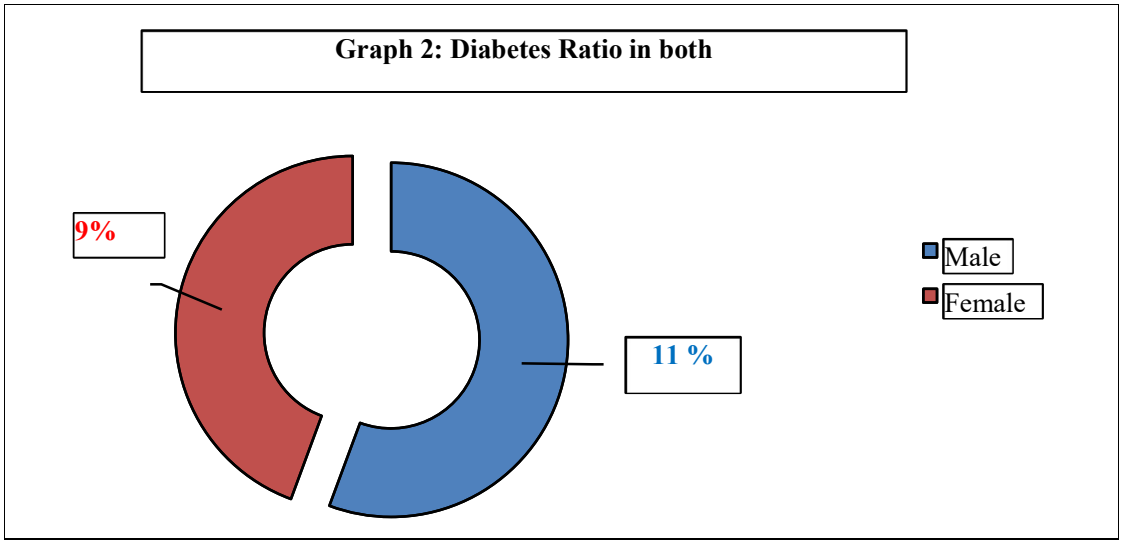

Figure 2: Graph shows diabeties patients' ratio in both gender

Table 1: Medicinal plants used in the treatment of Diabetes [9-5]

S. No.	Common name	Scientific name	Family	Parts used
1.	Arjunsal	*Terminelia arjuna*	Comberetaceae	Dried stem
2.	Aswagandha	*Withania somnifera*	Solanaceae	Roots, leaves
3.	Babhul	*Acacia Arabica*	Leguminaceae	Gummy exudation of stem and bark
4.	Brahmi	*Bacopa monniera*	Scrophulariaceae	Aerial parts
5.	Bitter gourd	*Mimordica chirantia*	Cucurbitaceae	Fresh green leaves
6.	Betel nut	*Areca catechu*	Palmitaceae	Dried ripe seeds
7.	Chirait	*Swertia chirata*	Gentinaceae	Entire herbs
8.	Gudmar	*Gymnema sylvestre*	Asclepidaceae	Dried leaves
9.	Guggul	*Commiphora mukul*	Burseraceae	Oleo gum resin incision of stem bark
10.	Kutas	*Pterocarpus marsupium*	Leguminaceae	Dried juice of plant
11.	Nagarmotha	*Cyprus rotandus*	Cyperaceae	Rhizome
12.	Pimpli	*Piper longum*	Piperaceae	Leaves
13.	Sunth	*Zingiber officinalis*	Zingiberaceae	Rhizome
14.	Tulsi	*Ocimum sanctum*	Labiateae	Entire herbs
15.	Yasti	*Glycyrrhiza glabra*	Leguminoceae	Roots, stolen

Table 2: List of herbal formulation available in market for the prevention of Diabetes [16-21]

S. No.	Marketed formulation	Manufacturer	Ingredients
1.	Asanand	Ayurveda Rasashala Pune	Ganasar, Arjuna, Lodhra, Karanja, Kanth, Shirish, Palash
2.	Adcaps	Doctors Pharmaceuticals	Haldi, Jambuphal, Amla, Mamajov, Neem, Karela, Vijaysar, Tejbal, Gulvel Sudha, Guggl, Trivang-Nag-Suvarnamakshik bhasm, Shilajeet, Ashok, Madhunasni
3.	Diabetic powder	Rahul Pharmacy Gujarat	Proprietary anti-diabetic herbs
4.	Gokshuradi guggul	Ayurveda Rasashala Pune	Gokshuradi guggul
5.	.Lohasava	Ayurveda Rasashala Pune	Lohabasma
6.	Giloysatva	Ayurveda Rasashala Pune	Giloysatva
7.	Indrajav churana	Indrajav churana	Universal Pharmacy Pune
8.	Shilajeet	Ayurveda Rasashala Pune	Shudha shilajeet
9.	Trivang bhasma	Ayurveda Rasashala Pune	Trivang bhasma
10.	Triphala guggul	Ayurveda Rasashala Pune	Triphala guggul

Nephropathy:- Nephropathy is the deterioration or decay of kidney function. The final stage of nephropathy is called kidney failure, end-stage renal disease (ESRD). According to the CDC, diabetes is the most common cause of ESRD. In 2011, about 26 million people in the U.S. were reported to have diabetes, and more than 200,000 people with ESRD due to diabetes were either on chronic renal dialysis or had a kidney transplant. Both type 1 and type 2 diabetes can lead to diabetic nephropathy, although type 1 is more likely to lead to ESRD. There are five stages of diabetic nephropathy. The fifth stage is ESRD. Progress from one stage to the next can take many years. high blood pressure, is a complication of diabetes that is believed to contribute most directly to diabetic nephropathy. Hypertension is believed to be both a cause of diabetic nephropathy, as well as a result of the damage that is created by the disease. As kidney disease progresses, physical changes in the kidneys often lead to increased blood pressure. Uncontrolled hypertension can make the progress toward stage five diabetic nephropathy occur more rapidly **[21-23]**.

The high blood sugar associated with diabetes also causes damage to the kidney through many different and complicated pathways. Most of this damage is directed toward the blood vessels that filter the blood to make urine

Symptoms of kidney disease:-

- Itching, dryness and crusts start forming in the skin due to kidney disease.
- The color of the skin becomes more white and itchy stretch marks appear.
- There is a deficiency of vitamins and minerals in the body due to which the nails look weak and white.
- Feeling of swelling in hands and feet.
- Some people start complaining of stomach ache and backache.
- Feeling of burning in urine also starts.

Those who sit in one place have more problems. Blood pressure and metabolism levels also deteriorate due to lack of

exercise. This also causes kidney diseases. More than 20% of kidney diseases are due to obesity alone. So make exercise a part of your daily routine **[24, 25]**.

Nephropathy in diabetes:- Diabetes has become the most common single cause of endstage renal disease (ESRD) in the US and Europe; this is due to the facts that 1) diabetes, particularly type 2, is increasing in prevalence; 2) diabetes patients now live longer; and 3) patients with diabetic ESRD are now being accepted for treatment in ESRD programs where formerly they had been excluded. In the US, diabetic nephropathy accounts for about 40% of new cases of ESRD, and in 1997, the cost for treatment of diabetic patients with ESRD was in excess of $15.6 billion. About 20–30% of patients with type 1 or type 2 diabetes develop evidence of nephropathy, but in type 2 diabetes, a considerably smaller fraction of these progress to ESRD. However, because of the much greater prevalence of type 2 diabetes, such patients constitute over half of those diabetic patients currently starting on dialysis. There is considerable racial/ethnic variability in this regard, with Native Americans, Hispanics (especially Mexican-Americans), and African-Americans having much higher risks of developing ESRD than non-Hispanic whites with type 2 diabetes. Recent studies have now demonstrated that the onset and course of diabetic nephropathy can be ameliorated to a very significant degree by several interventions, but these interventions have their greatest impact if instituted at a point very early in the course of the development of this complication. This position statement is based on recent review articles that discuss published research and issues that remain unresolved and provides recommendations regarding the detection, prevention, and treatment of early nephropathy **[12, 24-26, 28]**.

Quercetin:- Quercetin is characterized as a flavonol, one of the six subclasses of flavonoid compounds. Flavonoids are a family of plant compounds that share a similar flavone backbone (a three-ringed molecule with hydroxyl [OH] groups attached). A multitude of other substitutions can occur, giving rise to the subclasses of flavonoids and the different compounds found within these subclasses. Flavonoids also occur as either glycosides (with attached sugars [glycosyl groups]) or as aglycones (without attached sugars). Flavonols are present in a wide variety of fruits and vegetables. In Western populations, estimated daily intake of flavonols is in the range of 20-50 mg/day. Most of the dietary intake is as flavonol glycosides of quercetin, kaempferol, and myricetin rather than their aglycone forms **(Table 2)**. Of this, about 13.82 rag/day is in the form of quercetin-type flavonols **[29, 30]**.

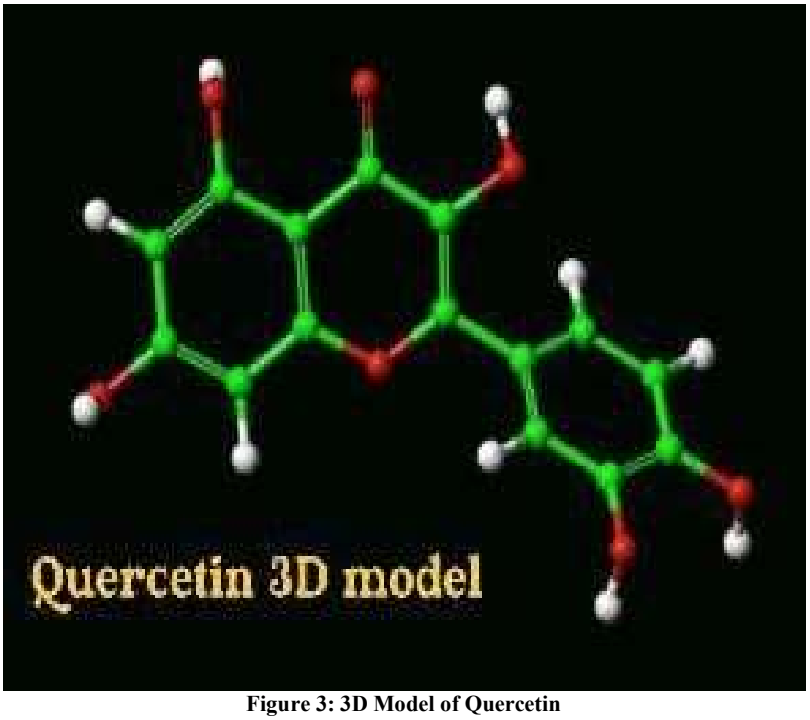

Figure 3: 3D Model of Quercetin

The variety of dietary flavonols is created by the differential placement of phenolic-OH groups and attached sugars. All flavonols, including quercetin, have in common a 3hydroxyflavone backbone. The determination of whether a flavonol is considered to be of the quercetin type as opposed to a kaempferol or myricetin type, for example, is based on the location of phenolic-OH groups.

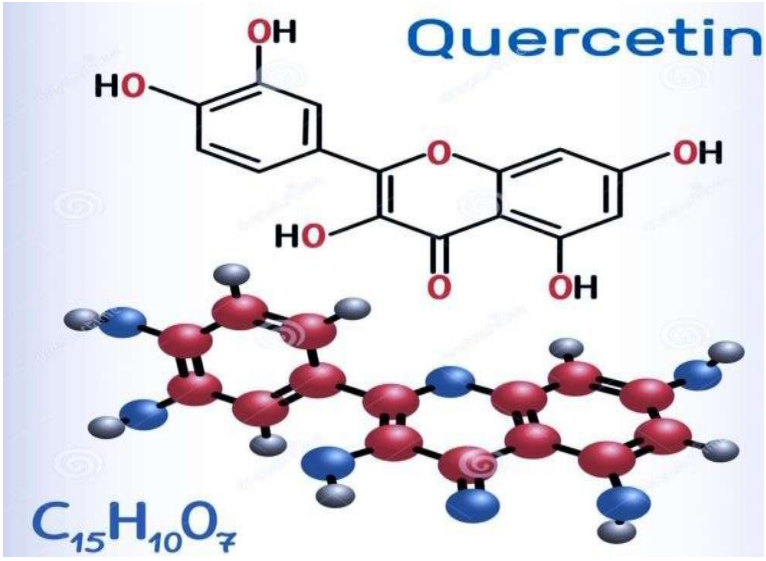

Figure 4: Structure of Quercetin

Figure 4 shows the possible attachment positions for hydroxyl and glycosyl groups. The International Union of Pure and Applied Chemistry (IUPAC)) nomenclature for quercetin is (3,3',4',5,7-pentahydroxyflavanone (or its synonym 3,3',4',5,7-pentahydroxy-2phenylchromen-4-one).

This means that quercetin has an OH group attached at positions 3, 5, 7, 3', and 4' **(Figure 2)**. The difference between quercetin and kaempferol is that the latter lacks the OH group at position 3'. The difference between quercetin and myricetin is that the latter has an extra OH group at position 5'. By definition quercetin is an aglycone, lacking an attached sugar. It is a brilliant citron yellow color and is entirely insoluble in cold water, poorly soluble in hot water, but quite soluble in alcohol and lipids. A quercetin glycoside is formed by attaching a glycosyl group (a sugar such as glucose, rhamnose, or rutinose) as a replacement for one of the OH groups (commonly at position 3). The attached glycosyl group can change the solubility, absorption, and in vivo effects. As a general rule of thumb, the presence of a glycosyl group (quercetin glycoside) results in increased water solubility compared to quercetin aglycone **[31-34]**.

The feature that distinguishes one quercetin glycoside from another is the type of glycosyl group attached. Hyperoside (found in St. John's wort) has a 3-O-galactoside group (an oxygen bonded to a galactoside group) at position 3 rather than an OH group. Isoquercitin (found in mangoes) has a 3-O-glucoside. Rutin (found in high amounts in buckwheat, citrus fruits, and Ruta graveolens) has an attached rutinose sugar at position 4. All of these are glycoside forms of quercetin (quercetin glycosides).

Technically, the term quercetin, Quercetin is found in high concentrations in asparagus, red onions, broccoli and buckwheat. Other names for quercetin include: Citrus bioflavonoid, Sophoretin; Meletin; Quercetine; Xanthaurine; Quercetol; Quercitin; Quertine; Flavin. Its powerful antioxidant and anti-inflammatory activities are well documented and are thought to play a role in treating and protecting against diseases including diabetes, cancer, neurodegenerative and cardiovascular diseases **[35, 36]**.

Figure 5: Content of Quercetin in various food material

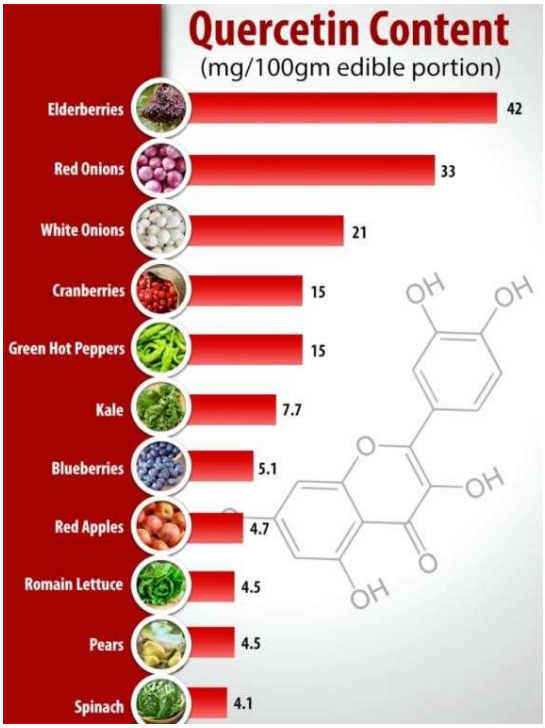

Figure 6: Content of Quercetin in various edible portion in per 100g

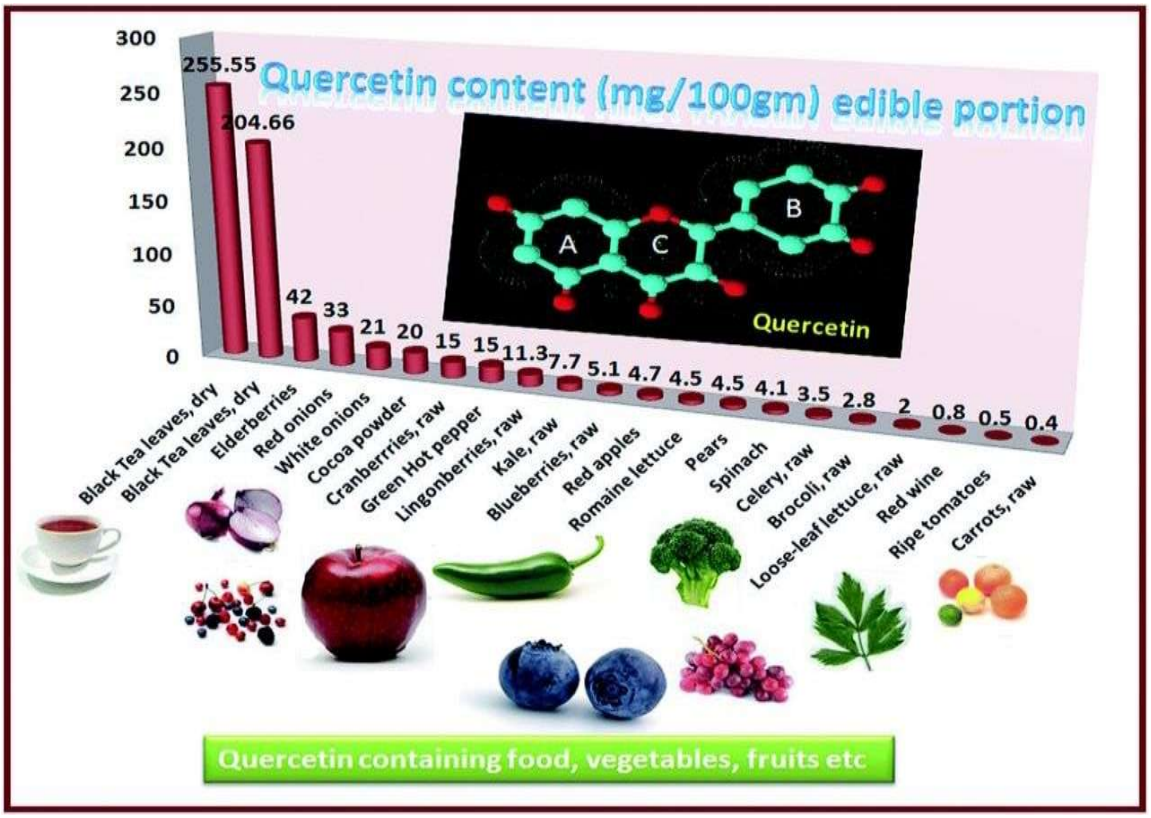

Figure 7: Content of Quercetin in various edible portion in per 100g

Metabolism:- Quercetin is rapidly metabolized (via glucuronidation) after the ingestion of quercetin foods or supplements. Five metabolites (quercetin glucuronides) have been found in human plasma after quercetin ingestion. Taken together, the quercetin glucuronides have a half life around 11-12 hours. In rats, quercetin did not undergo any significant phase I metabolism. In contrast, quercetin did undergo extensive phase II (conjugation) to produce metabolites that are more polar than the parent substance and hence are more rapidly excreted from the body. In vitro, the meta-hydroxyl group of catechol is methylated by catechol-O-methyltransferase. Four of the five hydroxyl groups of quercetin are glucuronidated by UDP-glucuronosyltransferase. The exception is the 5-hydroxyl group of the flavonoid ring which generally does not undergo glucuronidation. The major metabolites of orally absorbed quercetin are quercetin-3-glucuronide, 3'-methylquercetin-3-glucuronide, and quercetin-3'-sulfate. A methyl metabolite of quercetin has been shown in vitro to be more effective than quercetin at inhibiting lipopolysaccharide-activated macrophages. Compared to other flavonoids quercetin is one of the most effective inducers of the phase II detoxification enzymes. In-vitro studies show that quercetin is a strong inhibitor of the cytochrome P450 enzymes CYP3A4 and CYP2C19 and a moderate inhibitor of CYP2D6. Drugs that are metabolized by these pathways may have increased effect. An *in vivo* study found that quercetin supplementation slows the metabolism of caffeine to a statistically significant extent in a particular genetic sub-population, but in absolute terms the effect was almost negligible **[37, 41]**.

Pharmacological research:- Quercetin has been reported to inhibit the oxidation of other molecules and hence is classified as an antioxidant in vitro. It contains a polyphenolic chemical substructure that stops oxidation in vitro by acting as a scavenger of free radicals. Quercetin has been shown to inhibit the PI3K/AKT pathway leading to downregulation of the anti-apoptotic protein Bcl-w. Quercetin activates or inhibits the activities of a number of proteins in vitro. For example, it is a nonspecific protein kinase enzyme inhibitor **[38]**.

Sources of quercetin:- Fruits and vegetables are the primary dietary sources of quercetin, particularly citrus fruits, apples, onions, parsley, sage, tea, and red wine. Olive oil, grapes, dark cherries, and dark berries such as blueberries, blackberries, and bilberries are also high in quercetin and other flavonoids **[40]**.

Bananas are a great source of the super-protective compounds kaempferol and quercetin. These compounds have been

extensively studied, and are known to protect cells, reduce inflammation, fight numerous types of tumors, protect nerves, enhance blood circulation, and reduce the risk of a number of diseases **[39]**.

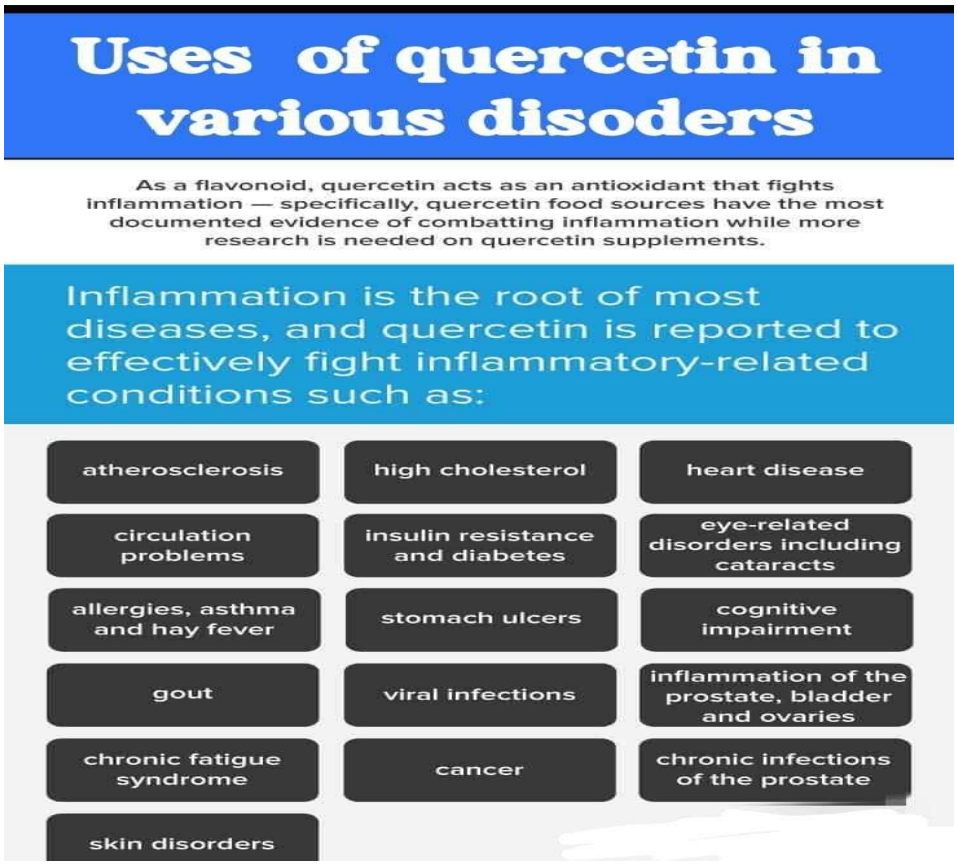

Figure 8: Uses of quercetin in various disorder

CONCLUSION:- Diabetes is a source of multiple disorder in which kidney disorder is an example. Now days there are many alternative medicines search for diabetes induced kidney disorder for that one maybe quercetin but more research needed to know its actual action on diabetes induce kidney disorder. There are various symptoms which indicate kidney disorder occurs during the period of diabetes treatment or suffering of this disorder.

REFERENCES:-

[1] Fideles, Simone Ortiz Moura, *et al*. "Influence of the Neuroprotective Properties of Quercetin on Regeneration and Functional Recovery of the Nervous System." Antioxidants 12.1 (2023): 149.

[2] Bala, Saroj, *et al*. "Transformation of agro-waste into value-added bioproducts and bioactive compounds: Micro/nano formulations and application in the

agri-food-pharma sector." Bioengineering 10.2 (2023): 152.

[3] Rachitha, Puttasiddaiah, *et al*. "Attenuation of Hyperlipidemia by Medicinal Formulations of Emblica officinalis Synergized with Nanotechnological Approaches." Bioengineering 10.1 (2023): 64.

[4] Singh, Priyanka, *et al*. "The role of quercetin in plants." Plant Physiology and Biochemistry 166 (2021): 10-19.

[5] Ezzati, Maryam, Bahman Yousefi, Kobra Velaei, and Amin Safa. "A review on anticancer properties of Quercetin in breast cancer." Life sciences 248 (2020): 117463.

[6] Foote J, Cohen B. Medicinal herb use and the renal patient. J Renal Nutr. 1998;8:40–2. [PubMed] [Google Scholar]

[7] Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR. *et al*. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996;334:1145–9. [PubMed] [Google Scholar]

[8] Shirzad H, Taji F, Rafieian-Kopaei M. Correlation between antioxidant activity of garlic extracts and WEHI-164 fibrosarcoma tumor growth in BALB/c mice. J Med Food. 2011;14:969–74. [PubMed] [Google Scholar]

[9] Wojcikowski K, Johnson DW, Gobé G. Medicinal herbal extracts -renal friend or foe? Part one: the toxicities of medicinal herbs. Nephrology (Carlton) 2004;9:313–8. [PubMed] [Google Scholar]

[10] Bartlett HE, Eperjesi F. Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial. Eur J Clin Nutr. 2007;64:1121–7. [PubMed] [Google Scholar]

[11] Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A. *et al*. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 1996;334:1150–5. [PubMed] [Google Scholar]

[12] A. K. Gupta, Quality Standards of Indian Medicinal Plants, ICMR, New Delhi, Vol. I, (1986) 168-173.

[13] Ansari SH. Essentials of Pharmacognosy. First edition. Birla Prakashan, Delhi - 32 (2005-2006) 588-590.

[14] Grover JK. Yadav S., Vats V. Medicinal plants in India with

antidiabetic potential. J. Ehnopharmacology. 2002; 81-100.

[15] Kokar R., Mantha S.V. Increased oxidative stress in rat liver & pancreas during progression of streptozotosin induced diabetes. J Clinical science.1998; 623-632.

[16] Kokate CK. Purohit AP. and Gokhale SB. Pharmacognosy, 11th edition, Nirali Prakashan (1999) 78-83.

[17] Shinde VM., Dhalwal K., Potdar M., Mahadik KR. Application of Quality Control Principles to Herbal Drugs. Int J Phytomed. 2009; 1:4- 14.

[18] Tripathi KD. Essential medical pharmacology, Sixth edition, (2007) 254-274.

[19] Agrawal, P; Ravi, V and Singh, RB (1996), "Randomized placebo controlled, single blind trial of holy basil Leaves in patients with noninsulin- dependent diabetes mellitus", International Journal of Clinical Pharmacoly & Therapeutics, 34, 406-409.

[20] Ahmed, I; Chandranath, AK, Sharma; E, Adeghate; DJ, Pallot and J, Singh (1999), "Mechanism of Hypoglycemic action of Momordica Charatia fruit juice in normal and diabetic rats", The Journal of Physiology, 520-525.

[21] Ailloux, Lionel (2007), "UpToDate Dialysis in diabetic nephropathy".

[22] Andier, Dusul; Tomer, Geaser (1990), "The antidiabetic activity of the bark of *Polyalthia longgifolia*", Journal of Agriculture and Food Chemstry, 17,704.

[23] Ang-Lee, MK; Moss, J; Yuan, CS, "Herbal medicines and perioperative care", JAMA,286.

[24] Antia, BS, "Coccina indica plants with hupoglycemic activity", Journal of Ethnopharmacology 26,1-55.

[25] Augusti, KT; Joseph, P; Babu, TD (1995), "Biologially active Principles isolated from salacia oblonga Wall", Indian Journal of Physiology and Pharmacology, 39, 415-417.

[26] Biswas & coworkers (1997), "To study Caesaplinia bonducella Methanol Alloxan Induced Diabetic Rats", Pharmaceutical Biology ,41, 5, 388-391.

[27] Blumenthal, M; Goldberg, A and Brinckmann (2000), "Herbal Medicine: Expanded Commission E Monographs Newton", Mass: Integrative Medicine Communications.

[28] Chakrabarti, D; Ghosh, A; Banerjee, N;Majumder, PC and

Gupta, M (1995), Plant .Res., 21-23,30.

[29] Chavez, ML; Chavez, PI (2000), "Herbal medicine. In: Novey DW, ed. Clinician's Complete Reference to Complementary and Alternative Medicine", St. Louis, Mo: Mosby, 545-563.

[30] Chhanda, Mallick; Rajkumar, Maiti and Debidas, Ghosh (2006), "Iranian Journal of Pharmacology & Therapeutics.

[31] Coon JT, Ernst E. (2002), "Panax ginseng: a systematic review of adverse effects and drug interactions", Drug Saf., 25 (5), 323-344.

[32] Sivaranjan, VV and Indira, Balachandran (2004) "Ayurvedic Drugs & their plant Source", 1st Edition Reprint-Oxford & IBH publishing Co. Pvt. Ltd., New Delhi.

[33] Sniderman, AD; Bhopal, R; Prabhakaran, D and Sarrafzadegan, N (2007), "Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis", International Journal of Epidemiology, 36 (1), 220-225.

[34] TK, Biswas; S, Bandyopadhyay;Biswapati, Mukherjee and BR, Sengupta(1997), "Oral Hypoglycemic effect of Caesalpina bonducella", International Journal of Pharmacognosy, 35,4,261-264.

[35] Trivedi, NA; Saxena, NS; Mazumdar, B; Bhatt, JD and Hemavathi, KG(2001),"Effect of Shilajit on blood glucose, lipid profile and vascular preparation inalloxan induced diabetic rats", Indian Journal of Pharmacology,143.

[36] Vinod D, Rangari (2007) "Pharmacognosy Phytochemistry", Vol.2, 1st Edition, Career Publication, Nashik,184.

[37] Serafini M, Morabito G. The Role of polyphenols in the modulation of plasma nonenzymatic antioxidant capacity (NEAC) Int J Vitam Nutr Res. 2012;82:228–32. [PubMed] [Google Scholar]

[38] Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and cause of death in the WHO multinational study of vascular disease in diabetes. Diabetologia. 2001;44:S14–21. [PubMed] [Google Scholar]

[39] Asif M. A brief study of toxic effects of some medicinal herbs on kidney. Adv Biomed Res.

2012;1:44. [PMC free article] [PubMed] [Google Scholar]

[40] Knight JA. Review: Free radicals, antioxidants, and the immune system. Ann Clin Lab Sci. 2000;30:145–58. [PubMed] [Google Scholar]

[41] Grodstein F, Kang JH, Glynn RJ, Cook NR, Gaziano JM. A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. Arch Intern Med. 2007;167:2184–90. [PubMed] [Google Scholar]