INTERLINKING PATHOPHYSIOLOGY- CORRELATION BETWEEN DIABETES MELLITUS AND MICROBIAL INFECTIONS: A PERSPECTIVE STUDY

(Word count: 2295)

MR. VIVEK KUMAR TIWARI (Assistant Professor, Gokaraju Rangaraju College of Pharmacy, Hyderabad, Telangana, India) -

Ramavath Binduja

Hannah Yancey Gujjarlapudi

Gurijala Sindhuja

(B.Pharmacy IV year, Gokaraju Rangaraju College of Pharmacy, Hyderabad, Telangana, India)

ABSTRACT:

The escalating dominance of Diabetes Mellitus poses a dual challenge with increased vulnerability to infections due to hyperglycaemia induced immune dysfunction. This study dwells into correlation between the underlying pathophysiology of Diabetes Mellitus and Microbial infection and the dual potential of drugs like Metformin, Thiazolidines and Quercetin in tackling both the diseases. Metformin mitigates effects by reducing ROS, improving cellular immunity and inhibiting biofilm formation. Thiazolidines modulate macrophage activation and reduces pro inflammatory cytokines to enhance insulin sensitivity and exhibits antimicrobial activity by inducing the breakdown of bacterial cell wall. Quercetin, a natural flavonoid improves insulin sensitivity, beta cell function and exhibits antimicrobial effects by membrane disruption and inhibition of microbial enzymes. This dual mechanism builds a foundation for innovative strategy in reducing medication burden by improving patient outcomes and in management of diabetic complications associated with infection.

KEYWORDS:

Diabetes Mellitus, Antimicrobial activity, Metformin, Thiazolidines, Quercetin, Immune modulation.

INTRODUCTION:

Diabetes mellitus is a global health concern, characterized by chronic hyperglycaemia due to impaired insulin secretion or action. This condition not only leads to long-term complications like cardiovascular disease and neuropathy but also increases susceptibility to infections, owing to compromised immune defences. The hyperglycaemic state disrupts innate and adaptive immunity by impairing neutrophil activity, reducing phagocytosis, and altering cytokine profiles, which collectively weaken the body's resistance to pathogens. Furthermore, elevated glucose levels create a favourable environment for microbial growth, particularly increasing the virulence of bacteria like Staphylococcus aureus and Candida albicans. Recent studies have shown that certain antidiabetic drugs may possess antimicrobial properties, potentially providing dual benefits in managing both hyperglycaemia and infections. This review aims to explore the intricate link between the pathophysiology of diabetes and antimicrobial resistance, examining molecular pathways that can be targeted for novel therapeutic strategies.

PATHOPHYSIOLOGY OF DIABETES MELLITUS:

Diabetes mellitus is primarily characterised into two types- Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). While T1DM is an auto-immune condition where the immune system attacks and destroys insulin-producing beta cells in the pancreas, T2DM is a disorder of insulin resistance, with a relative insulin deficiency that develops over time and is closely associated with obesity, physical inactivity, and genetic predisposition.

In T1DM, the main defect is the autoimmune destruction of the insulin producing B cells in the islets of Langerhans. This mechanism usually is triggered by a number of environmental factors such as viral infections and genetically predisposed individuals. As the beta cells keep getting destroyed, the insulin production becomes low and in the absence of insulin, the cells cannot intake glucose and the glucose remains in the bloodstream. Therefore, it results in the inability of the body to maintain adequate blood glucose levels.

In T2DM, insulin resistance coupled with beta-cell dysfunction results in relative insulin deficiency. In this condition, the body tissues do not respond to insulin activity and therefore cannot intake glucose. Following this, the beta cells secrete more and more insulin to which the body tissue cells still remain unresponsive. This subsequently leads to beta cells fatigue and also elevated blood glucose levels. Such hyperglycaemic conditions result in immunity dysfunction. Metabolic irregularities and also some inflammatory effects. Chronic low-grade inflammation is common in T2DM. Inflammatory cytokines (e.g., TNF-α, IL-6) produced by adipose tissue contribute to insulin resistance and beta-cell dysfunction.

PATHOPHYSIOLOGY OF MICROBIAL INFECTIONS:

Following the infection and invasion by a microbial pathogen, our body follows certain pathways to trigger an immunological or inflammatory response in order to eliminate the pathogen. In cases of bacterial infections, the body initially responds with inflammation, involving neutrophils, macrophages, and dendritic cells. The release of cytokines (e.g., TNF-α, IL-1) leads to fever, tissue swelling, and recruitment of more immune cells to the infection site. If the infection persists, the adaptive immune system (T cells, B cells, and antibodies) is activated to provide a more targeted response.

CORRELATION BETWEEN THE PATHOPHYSIOLOGY OF DIABETES AND MICROBIAL INFECTIONS:

The correlation between the pathophysiology of diabetes mellitus and microbial infections primarily occurs on three levels- Immunological, Metabolic and Inflammatory.

This mutual interlink is observed right at the conception of diabetes wherein the T-cell mediated immune response lead to the destruction of pancreatic β- cells causing T1DM. The presence of one or more risk factors in diabetes result in a series of immune reactions. These include the loss of tolerance to the pancreatic β-cell antigen, production of antidiabetic antibodies by plasma β-cells and activation of harmful CD4 and CD8 T cells. This leads to gradual damage of pancreatic β-cells. This autoimmune process often goes unnoticed until significant damage to the pancreatic islets occurs at which point high blood sugar develops and the person becomes insulin dependent.

On the other hand, it can also be observed that the gut microbiota plays an undeniable role in many metabolic disorders such as diabetes and certain immunological responses. Some gut microbiota members such as *Ruminococcus, Fusobacterium, Balutia* and *Firmicutes,* have been linked to poor glucose regulation and a higher risk of obesity and diabetes. At the genus level, Roseburia, a butyrate-producing bacterium crucial for maintaining gut health and insulin sensitivity, is consistently less abundant in T2DM patients. Conversely, Lactobacillus spp., associated with immunomodulatory roles and higher blood glucose levels, is enriched in these individuals. This dysbiosis is linked to an altered immune response, as Gram-negative bacteria, capable of activating toll-like receptors (TLRs), are more abundant in T2DM. Increased TLR activation, especially TLR-4 and TLR-5, has been shown to exacerbate insulin resistance in both animal and human studies.

Patients diagnosed with diabetes mellitus exhibit 4 different irregularities that lead them to be susceptible to microbial infections. They are;

A) Immune dysfunction
B) Chronic Inflammation
C) Metabolic dysregulation
D) Microbiome alteration

- In individuals with hyperglycaemia, characterised by elevated blood glucose levels, a significant decline in their immunity can be observed. This dysfunction is manifested by impaired activity of neutrophils, macrophages, lymphocytes. Additionally reduced phagocytosis and altered cytokine production can also be observed.
- Chronic inflammation can be observed in DM patients due to the triggering of proinflammatory pathways. These pathways lead to creation of a pathological feedback loop characterised by increased insulin resistance which further perpetuates metabolic dysregulation and increases risk of complications.
- In DM conditions, due to activation of the polyol pathway, the antioxidant activity decreases leading to the cells facing oxidative stress. This stress creates a significant damage to the cells thereby compromising tissue integrity and making the diabetic individuals vulnerable to infections.
- Diabetes is frequently associated with delayed wound healing primarily due to poor blood circulation and neuropathy. These factors lead to reduced tissue healing capacity making them an easy target for any infections such as UTIs, skin and respiratory infections.
- Due to increased permeability of intestinal barrier in diabetic conditions, it causes significant alterations in the gut microbiome. These changes result in heightened systemic inflammation, contributing to pathogenesis of various secondary complications such as gum infections.

POTENTIAL DUAL ACTION OF ANTIDIABETIC DRUGS:

- **Metformin:**

It is the first-line of pharmacotherapy for type 2 diabetes mellitus (T2DM). Metformin works by reducing insulin resistance and causes significant reduction in plasma fasting insulin levels. Metformin primarily reduces the amount of glucose produced by the liver by inhibiting the mitochondrial respiratory chain which activates AMPK (Adenosine Monophosphate- activated Protein Kinase) and reduces expression of gluconeogenic enzymes. Subsequently, it also reduces the amount of glucose absorbed from food and increases the body's response to insulin. Metformin has a very complex mechanism of action and usually works by inhibiting hepatic GPD2 activity, blocking the synthesis of endogenous fatty acids and regulating mTOR pathway.

Recent research suggests that the gut and its microbiome may play a pivotal role in the drug's effects, especially given that metabolic disorders, including T2DM, are often associated with gut dysbiosis. Metformin can increase the production of Short chain Fatty acids which can help in regulating the balance of intestinal microbiota, improve intestinal immune function and maintain electrolyte balance. Studies indicate that metformin not only affects glucose metabolism directly but also alters the gut microbiota composition, providing new insights into its therapeutic potential. Metformin can be an effective drug during microbial infections as well through the below activities-

- It disrupts the outer membrane of bacteria or their cell wall making it easier for the penetration of antibiotics.
- It reduces the inflammatory response caused by the microbial infection.
- It can improve the phagocytic function of immune cells and reduce the neutrophil-lymphocyte ratio.
- It can increase the expression of antimicrobial peptides such as RNase 7 Cathelicidin LL-37, which can act both intracellularly and extracellularly.

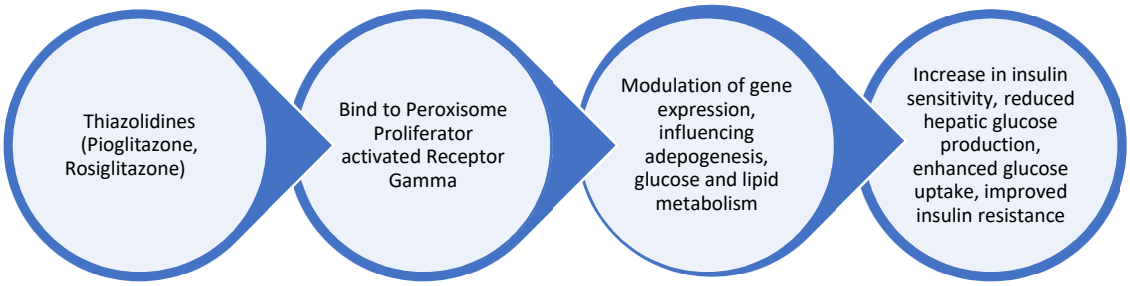
Metformin and the Gut Microbiota -

Rodent studies suggest mechanisms through which metformin improves glucose metabolism via the microbiome, including increased production of short-chain fatty acids (SCFAs), enhanced intestinal barrier integrity, and modulated bile acid metabolism. SCFAs, such as butyrate and propionate, improve insulin sensitivity and reduce systemic inflammation, mitigating insulin resistance. Clinical studies corroborate these findings, demonstrating a significant increase in SCFA-producing bacteria and improved glycemic control in metformin-treated T2DM patients.

- **Thiazolidines:**

Thiazolidines like pioglitazone, rosiglitazone etc. shows anti diabetic activity by transactivation of PPAR (Peroxisome proliferated activated receptor-gamma). PPAR binds with thiazolidine and reacts with retinoid X factor (RXR) to form the PPAR-RXR complex, which binds with PPRE's (Peroxisome proliferator response elements) along with histone acetylase activity containing co activator in the target gene which in turn aid the transcription of gene in cellular differentiation and glucose, lipid metabolism causing improved insulin

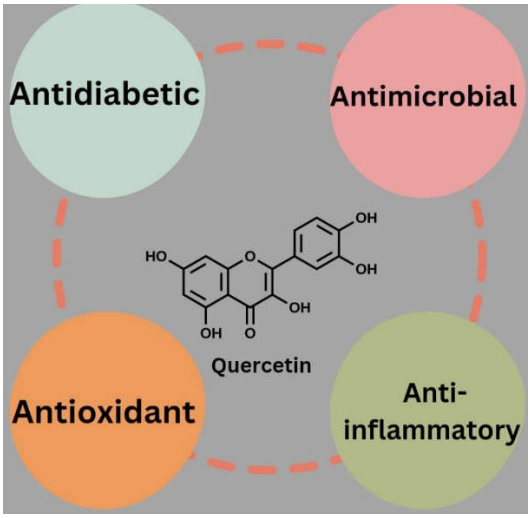
resistance and therefore lowers blood glucose levels in type-2 diabetes disease.



On the other hand, the antimicrobial activity of thiazolidines can be manifested by its ability to inhibit the bacterial cell wall formation. Bacterial cell wall plays a major role in cell protection and maintaining shape of the cell. It consists of peptidoglycan as major constituent. Cell death occurs due to inhibition of its biosynthetic enzymes like penicillin binding proteins which are membrane bound extracellular enzymes or Mur enzymes which are cytoplasmic. 4 cytoplasmic ATP dependent enzymes known as Mur ligases (Mur C-F) are involved in peptidoglycan peptide stem biosynthesis. Addition of Mur C (L-alanine), Mur D (D-glutamic acid) or Mur E (L-lysine) and Mur F (dipeptide D-Ala-D-Ala) to D-lactoyl group of UDP-N-acetylmuramic acid forms UDP-MurNAc pentapeptide which helps in peptidoglycan biosynthesis. Thiazolidines inhibit these ligases leading to inhibition of peptidoglycan synthesis causing cell death thereby showing antibacterial activity.

- **Quercetin:**

Among 4000 variations in Flavonoids present in nature, the class Flavanols contain Quercetin (chemically, 3,5,7,3',4'- Pentahydroxy flavone) which has potential dual action as Antidiabetic and Antimicrobial.



Quercetin class of flavonoids exhibit Antidiabetic action by blocking protein kinases & cyclooxygenases (COX) enzymes which in turn inhibits Apoptosis & Cell proliferation. In addition to it, Quercetin also promotes beta cell regeneration in pancreatic islets which upregulates insulin & normalizes blood sugar levels. Quercetin present in *Prunus persica* (Peach) through in vitro studies produced Antidiabetic action along with Antioxidant & Antiadipogenic effects. Ethyl acetate leaf extract of doses 100 & 20 mg/kg per oral when given to Streptozotocin (STZ) induced diabetic rat models, revealed that there is reduction in Hyperglycemic levels & also improvement in lipid profile and body weight.

In an investigation of 2 enzymes expression in glucose metabolism namely Glucose -6-phosphatase & Glucokinase when experimented on 24 adult Wistar Rats divided into 3 groups (Control, Streptozotocin - induced diabetic rats & Quercetin treated groups) given 15 mg/ kg through peritoneal route. On the 21-day treatment period this investigation revealed a significant decrease in blood glucose and malondialdehyde levels in the Quercetin treated group.

Furthermore, Quercetin produces antibacterial activity by inhibiting beta- ketoacyl carrier protein synthesis which are involved in bacterial fatty acid synthesis & also by removal of the biofilm. Antifungal activity is produced by decreasing the cell adhesion & inhibition of biofilm formation, by disrupting the plasma membrane, inhibition of cell wall, cell division, inhibition of efflux system.

Invitro studies against the S. aureus using various organic extracts & In silico studies in 4 different bacteria (Gama Hemolysins, DNA primases, Peptide deformylase & Undecaprenyl pyrophosphate synthase) with the aid of AutoDock Vina 1, has confirmed that the metabolic

extracts of 20 mg/ml of Quercetin inhibits the complete growth of S. aureus. In silico studies concludes that Quercetin is found to be the auxiliary metabolite which hinders the proteins of S.aureus (Peptide deformylase, Undecaprenyl pyrophosphate & DNA primases). Microdilution Method determination of MIC values revealed the inhibition of biofilm formation & Antibacterial Properties of Quercetin in the species of S.aureus, S.sapropyticus etc. Another study reveals that Quercetin along with 6 organic acids (Rosamaric acid, Citric chlorogenics, Salicylic acid, Quinic acid, Malic acid) exhibits antimicrobial activity to a greater extent against Gram negative bacteria than Gram positive bacteria.

- **Probiotics and Microbiota Transplantation:**

Probiotics have shown potential in reducing systemic lipopolysaccharide (LPS) levels and improving insulin sensitivity in T2DM patients. Additionally, fecal microbiota transplantation (FMT) from healthy donors has been reported to increase Roseburia abundance and enhance insulin sensitivity in recipients with metabolic disorders.

CONCLUSION:

In conclusion, the intricate relationship between the pathophysiology of Diabetes Mellitus and Microbial infections underscores the significant impact between of hyperglycemia on immune dysfunction, chronic inflammation, metabolic dysregulation and microbiome alteration, all of which contribute to increased susceptibility to infections in diabetic patients. Research has demonstrated that in individuals with diabetes, immune cell function is impaired, neutrophils exhibit reduced phagocytic activity and inflammation is often exacerbated, creating a pathological cycle that worsens glucose control and increases infection risk. Through this review, understanding the above mechanisms has highlighted the potential of certain antidiabetic drugs such as metformin, thiazolidines and quercetin, to not only manage blood glucose but also offer antimicrobial benefits. By targeting both metabolic and immune pathways, these therapies may provide a dual approach to addressing the challenges of diabetic-related infections, paving the way to more comprehensive treatment strategies that not only control blood glucose but also protect against infections, thereby improving patient outcomes.

REFERENCES:

1. Naim, M.J.; Alam, M.J.; Ahmad, S.; Nawaz, F.; Shrivastava, N.; Sahu, M.; Alam, O. Therapeutic journey of 2,4-thiazolidinediones as a versatile scaffold: An insight into structure activity relationship. Eur. J. Med. Chem. 2017, 129, 218–250. [CrossRef] [PubMed]
2. Kumar, H.; Deep, A.; Marwaha, R.K. Chemical Synthesis, Mechanism of Action and Anticancer Potential of Medicinally Important Thiazolidin-2,4-dione Derivatives: A Review. Mini. Rev. Med. Chem. 2019, 19, 1476–1516. [CrossRef] [PubMed]
3. Clin Pharmacol. 2021 May 11; 13:83–90. doi: 10.2147/CPAA.S297903, Metformin as a Potential Adjuvant Antimicrobial Agent Against Multidrug Resistant Bacteria: Majed M Masadeh, Karem H Alzoubi, Majd M Masadeh , Zainah O Aburashed.
4. World J Diabetes. 2021 Nov 15;12(11):1832–1855. doi: 10.4239/wjd.v12.i11.1832, Anti-diabetics and antimicrobials: Harmony of mutual interplay: Wael A H Hegazy, Azza A H Rajab, Amr S Abu Lila, Hisham A Abbas
5. Bansal, G.; Singh, S.; Monga, V.; Thanikachalama, P.V.; Chawla, P. Synthesis and biological evaluation of thiazolidine-2,4-dione- pyrazole conjugates as antidiabetic, anti-inflammatory and antioxidant agents. Bioorg. Chem. 2019, 19, 103271. [CrossRef] [PubMed]
6. Mahapatra, M.K.; Kumar, R.; Kumar, M. Exploring sulfonate esters of 5-arylidene thiazolidine-2,4-diones as PTP1B inhibitors with anti-hyperglycemic activity. Med. Chem. Res. 2018, 27, 476–487. [CrossRef]
7. Sucheta; Tahlan, S.; Verma, P.K. Synthesis, SAR and in vitro therapeutic potentials of thiazolidine-2,4-diones. Chem. Cent. J. 2018, 12, 129.
8. Abdellatif, K.R.; Fadaly, W.A.; Kamel, G.M.; Elshaier, Y.A.; El-Magd, M.A. Design, synthesis, modeling studies and biological evaluation of thiazolidine derivatives containing pyrazole core as potential anti-diabetic PPAR-γ agonists and anti-inflammatory COX-2 selective inhibitors. Bioorg. Chem. 2019, 82, 86–99. [CrossRef]
9. Elkamhawy, A.; Kim, N.Y.; Hassan, A.H.E.; Park, J.E.; Paik, S.; Yang, J.E.; Oh, K.S.; Lee, B.H.; Lee, M.Y.; Shin, K.J.; et al. Thiazolidine-2,4-dione-based

irreversible allosteric IKK-β kinase inhibitors: Optimization into in vivo active anti-inflammatory agents. Eur. J. Med. Chem. 2020, 188, 111955. [CrossRef]

10. Asati, V.; Bajaj, S.; Mahapatra, D.K.; Bharti, S.K. Molecular Modeling Studies of Some Thiazolidine-2,4-Dione Derivatives as 15-PGDH Inhibitors. Med. Chem. Res. 2015, 25, 94–108. [CrossRef]
11. Yu, I.; Choi, D.; Lee, H.-K.; Cho, H. Synthesis and Biological Evaluation of New Benzylidenethiazolidine-2,4-Dione Derivatives as 15-Hydroxyprostaglandin Dehydrogenase Inhibitors to Control the Intracellular Levels of Prostaglandin E2 for Wound Healing. Biotechnol. Bioprocess Eng. 2019, 24, 464–475. [CrossRef]
12. Upadhyay, N.; Tilekar, K.; Jänsch, N.; Schweipert, M.; Hess, J.D.; Henze Macias, L.; Mrowka, P.; Aguilera, R.J.; Choe, J.; Meyer-Almes, F.-J.; et al. Discovery of novel N-substituted thiazolidinediones (TZDs) as HDAC8 inhibitors: In-silico studies, synthesis, and biological evaluation. Bioorg. Chem. 2020, 100, 103934. [CrossRef]
13. El-Kashef, H.; Badr, G.; Abo El-Maali, N.; Sayed, D.; Melnyk, P.; Lebegue, N.; Abd El-Khalek, R. Synthesis of a novel series of (Z)-3,5-disubstituted thiazolidine-2,4-diones as promising anti-breast cancer agents. Bioorg. Chem. 2020, 96, 103569. [CrossRef] [PubMed]
14. Abdelgawad, M.A.; El-Adl, K.; El-Hddad, S.S.A.; Elhady, M.M.; Saleh, N.M.; Khalifa, M.M.; Khedr, F.; Alswah, M.; Nayl, A.A.; Ghoneim, M.M.; et al. Design, Molecular Docking, Synthesis, Anticancer and Anti-Hyperglycemic Assessments of Thiazolidine- 2,4-diones Bearing Sulfonylthiourea Moieties as Potent VEGFR-2 Inhibitors and PPAR Agonists. Pharmaceuticals 2022, 15, 226. [CrossRef]
15. Taghour, M.S.; Elkady, H.; Eldehna, W.M.; El-Deeb, N.M.; Kenawy, A.M.; Elkaeed, E.B.; Alsfouk, A.A.; Alesawy, M.S.; Metwaly, A.M.; Eissa, I.H. Design and synthesis of thiazolidine-2,4-diones hybrids with 1,2-dihydroquinolones and 2-oxindoles as potential VEGFR-2 inhibitors: In-vitro anticancer evaluation and in-silico studies. J. Enzym. Inhib. Med. Chem. 2022, 37, 1903–1917. [CrossRef]
16. El-Adl, K.; Sakr, H.; El-Hddad, S.S.; El-Helby, A.G.; Nasser, M.; Abulkhair, H.S. Design, synthesis, docking, ADMET profile, and anticancer evaluations of

novel thiazolidine-2,4-dione derivatives as VEGFR-2 inhibitors. Arch. Pharm. 2021, 354, 2000491. [CrossRef] [PubMed]

17. Sharma, R.K.; Younis, Y.; Mugumbate, G.; Njoroge, M.; Gut, J.; Rosenthal, P.J.; Chibale, K. Synthesis and structure activity- relationship studies of thiazolidinediones as antiplasmodial inhibitors of the Plasmodium falciparum cysteine protease falcipain-2. Eur. J. Med. Chem. 2015, 90, 507–518. [CrossRef] [PubMed]
18. World J Diabetes. 2019 Mar 15;10(3):154–168. doi: 10.4239/wjd.v10.i3.154, Crosstalk between gut microbiota and antidiabetic drug action: Yevheniia Kyriachenko, Tetyana Falalyeva, Oleksandr Korotkyi , Nataliia Molochek, Nazarii Kobyliak
19. Nat Rev Gastroenterol Hepatol. Author manuscript; available in PMC: 2023 Aug 1. Published in final edited form as: Nat Rev Gastroenterol Hepatol. 2022 Oct 18;20(2):81–100. doi: 10.1038/s41575-022-00685-9. Antibiotics in the pathogenesis of diabetes and inflammatory diseases of the gastrointestinal tract: Aline C Fenneman , Melissa Weidner , Lea Ann Chen , Max Nieuwdorp, Martin J Blaser.
20. Nasrin, Fatema. "Study of Antimicrobial and Antioxidant Potentiality of Anti-diabetic Drug Metformin." International Journal of Pharmaceutics and Drug Analysis, vol. 2, no. 3, 21 Mar. 2014, pp. 220-224.
21. 1.Ozgen S, et al. Antioxidant action of quercetin: a mechanistic review. Turk J Agric- Food Sci Technol. 2816; 4 (12): 1134-1138.
22. Xu D, et al. Antioxidant Action of quercetin and it's complexes for medicinal application 2019; 24(6): 1124 - PMC Pub Med.
23. Srimathi pryinaga K, vijayalakshmi K. Investigation of Antioxidant potential of quercetin & hesperidin: an invitro approach. Asian J pharm clin Res. 2017; 10:83-86.
24. Farhadi F, et al. Antibacterial activity of Flavonoids & their structure activity relationship: an update review. Phytother Res. 2019, 33 (1) : 13- 40. Pub Med.
25. Mortale S, karuppayil S. Review on combinatorial approach for inhibiting Candida albicans biofilm. Am J Clin Microbial Antimicrobial. 2018; 1:1 - 10
26. AI Aboody MS, Mickymaray SJD. Antifungal efficacy & Mechanisms of Flavonoids. Antibiotics. 2020; 9 (2): 45 - PMC- Pub Med.

27. Lalani S, Poh (EV - A 71) Viruses. 2020; 12 (2): 184 - PMC Pub Med.
28. Coloung Biancatelli RML; et al. Quercetin & Vitamin C: an experimental, synergistic therapy for the prevention & treatment of SARS - COV -2 related disease (COVID-19), Front Immunol. 2020; 11:1451. PMC - Pub Med.
29. Boudiaf F, et al. Antidiabetic role of quercetin & cinnamon on neuro behavioural alterations & biochemical parameters of induced diabetes rats J Anim Behav Biometerol. 2020; 8 (3): 190-195.
30. Sharma G et al (2018) Antidiabetic, antioxidant, Antiadipogenic potential of quercetin rich ethyl acetate fraction of Prunes persica. Pharmacognosy. J 10(3).