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SYNTHETIC STRATEGIES, PHARMACOLOGICAL ACTIVITY, AND STRUCTURE-ACTIVITY RELATIONSHIP OF QUERCETIN AND ITS DERIVATIVES: A REVIEW

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Abstract

Quercetin (3,4',7,5,3'-pentahydroxylflavone) is a flavonol and it belongs to the group of flavonoids that are secondary metabolic products found in plants, which is widely distributed in various fruits and vegetables. According to the growing data, quercetin may be therapeutically useful in treating and preventing a variety of disorders. On the basis of many research reports, quercetin was found to possess a broad spectrum of pharmacological properties. There are several synthetic as well as natural protocols for quercetin synthesis, also it includes a lot of pharmacological activity, but its low solubility and bioavailability limit its therapeutic potential. Any small change in the structure of the medicinal compounds may cause a major change in the bioavailability and pharmacological action. This article aimed to investigate the pharmacological activity and the structure-activity relationship of quercetin and its derivatives.

Keywords: Quercetin, Flavonoids, Derivatives, Biological Activity, Structure-Activity Relationship.

1. INTRODUCTION

Quercetin (3,7,5,3',4'-pentahydroxy flavone) which gets its name from the Quercus-related quercetum (oak forest), has been extensively used since 1857. In nature, there are numerous flora that contain quercetin, including those that grow grapes, brassica, onions, apples, herbal tea, spring onions, capers, tomatoes, berries, as well as several nuts, flower petals, seeds, tree bark, and leaves. Molecular formula of quercetin is $C_{15}H_{10}O_7$ **[1]**. The blood-brain barrier (BBB) can be crossed by quercetin as it undergoes a first-pass metabolic process **[2]**.

Quercetin is a flavonoid that is moderately hydrophilic and water soluble. A major barrier to its medicinal usage is still its poor solubility in water, which is specifically tied to its poor bioavailability **[3]**. The primary cause of this is the dense inter-molecular arrangement of planar phenol and hetero rings, however, it is possible to break up this intermolecular packing and increase flavonol elimination by reducing the hydroxyl group of flavonols using an acyl donor that contains a short aliphatic backbone **[4]**.

It possesses numerous biological properties such as anti-tumor **[5]**, anti-inflammatory **[6]**, antioxidant **[7]**, hepatoprotection **[8],** anti-hypertensive **[9]**, anti-viral **[10]**, anti-tubercular **[11]**, anticonvulsant **[12]**, anti-microbial, as mentioned in **Fig.1 [13]**.

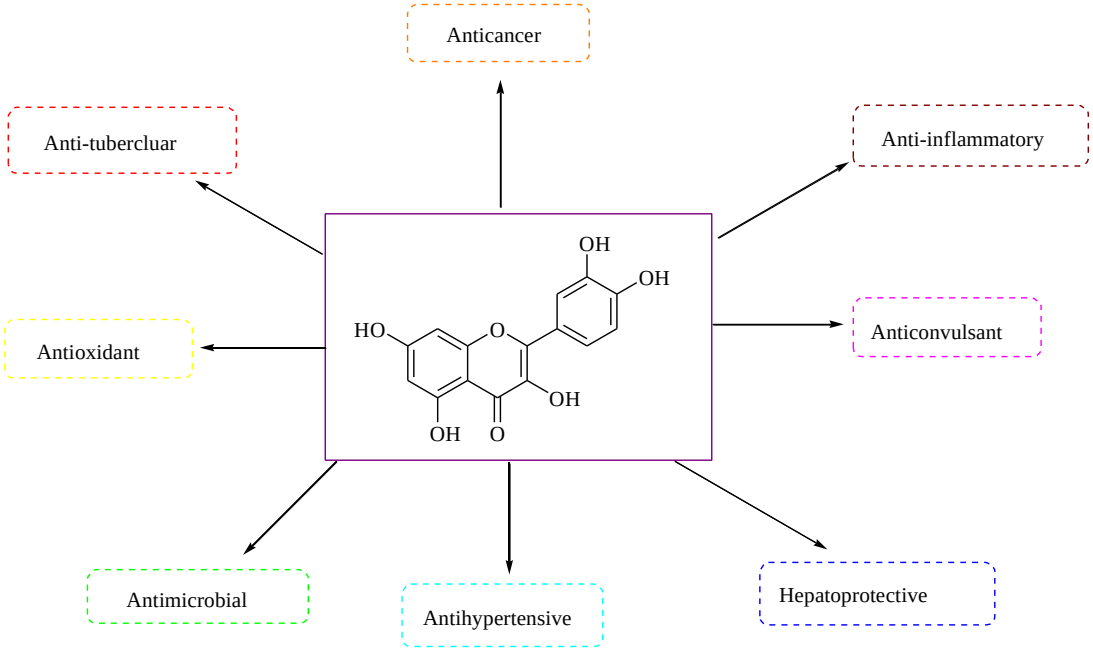


Fig 1: Pharmacological activity of Quercetin

2. SAR OF QUERCETIN

The essential components of the molecule include a polyhydroxylated A and B aromatic structure, a dual bonding among the second and third carbons, a carbonyl group in the 4th carbon, and a third-carbon alcohol group. Two OH groups are present in ring B **[14]**. The effectiveness of flavonoids in different roles like fighting cancer, acting as antioxidants, managing diabetes, and reducing inflammation becomes more pronounced when more hydroxyl (OH) groups are present. Conversely, an elevate in the OH groups tends to lower their antiviral and antibacterial properties **[15]**.

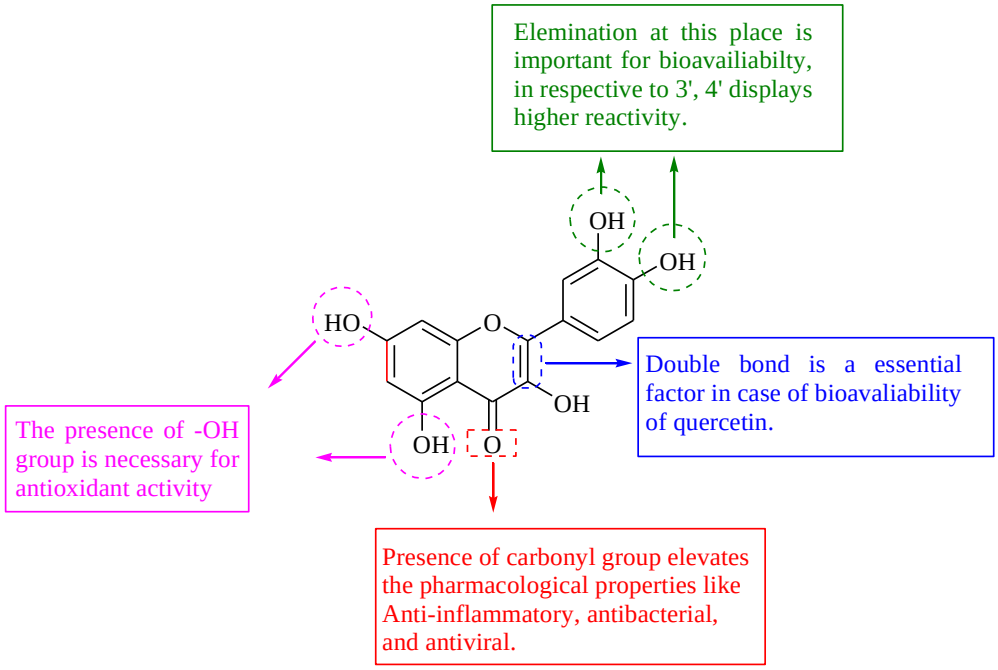
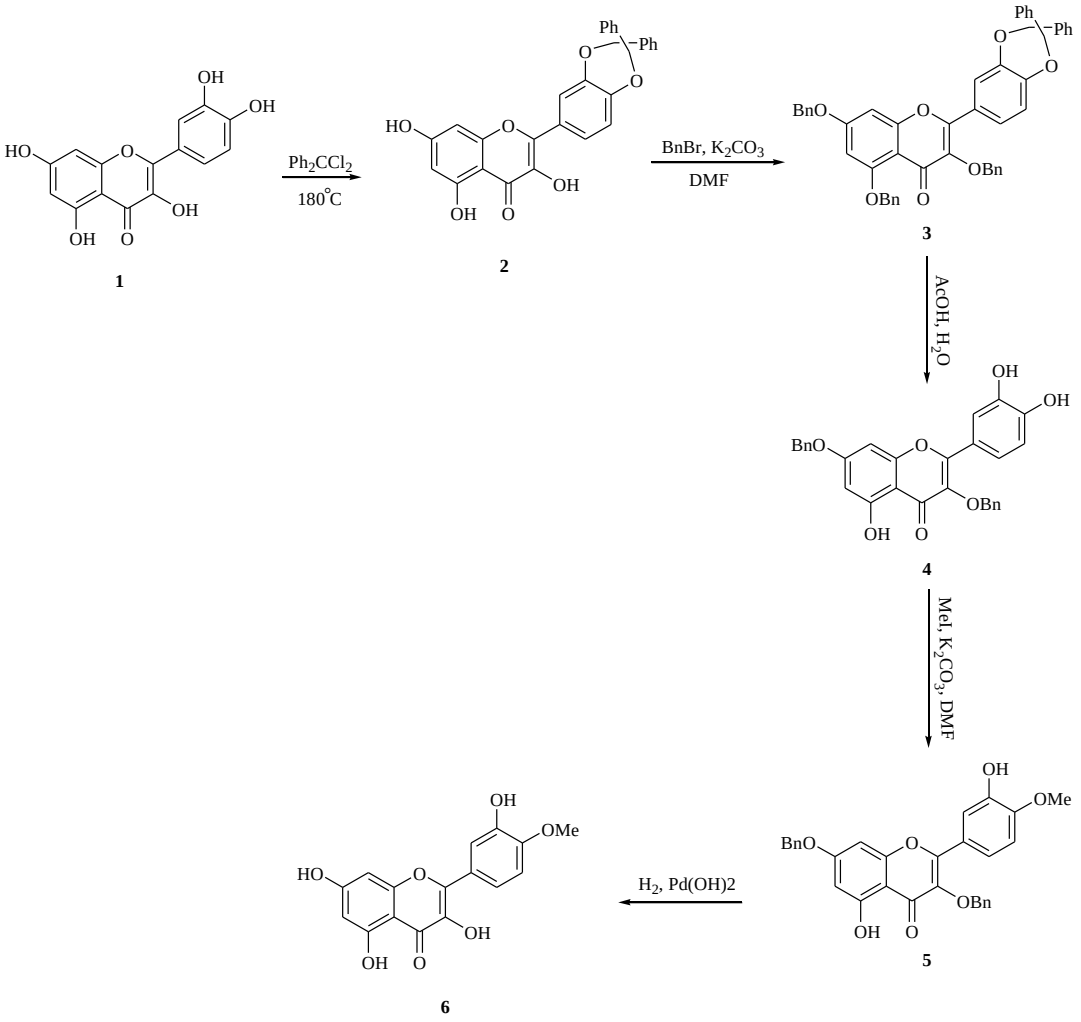


Fig 2: Structure-activity relationship of quercetin

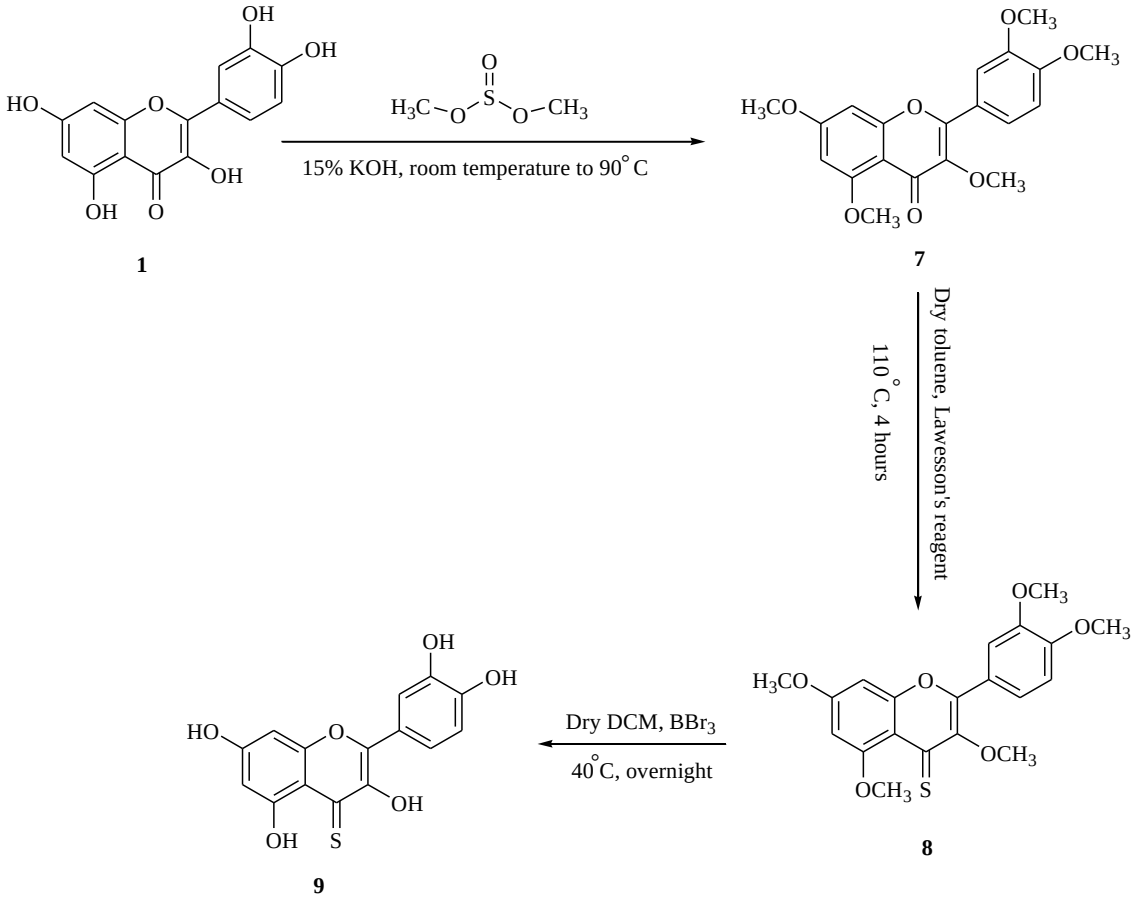
3. SYNTHESIS STRATEGIES

Hirpara K V et al. synthesized 4'-O-methyl quercetin (Tamarixetin) (**6**) followed by the reaction by employing dichlorodiphenylmethane, K_2CO_3 in acetonitrile at 180^0 C to effectively protect the catechol ring of quercetin (**1**), the product obtained (**2**) was then benzylated in the presence of K_2CO_3, benzyl bromide in DMF to produce 3,5,7-tribenzylated quercetin (**3**). By deprotecting the catechol ring and particularly debenzylating its 5-hydroxy group with an acetic acid/ water solution, 3,7-dibenzylated quercetin (**4**) was synthesized. Effectively methylation of the 4'-hydroxy group leads to the formation of compound (**5**) and further the debenzylation of (**5**) gives the final product **6**, shown in **Scheme 1 [16]**.



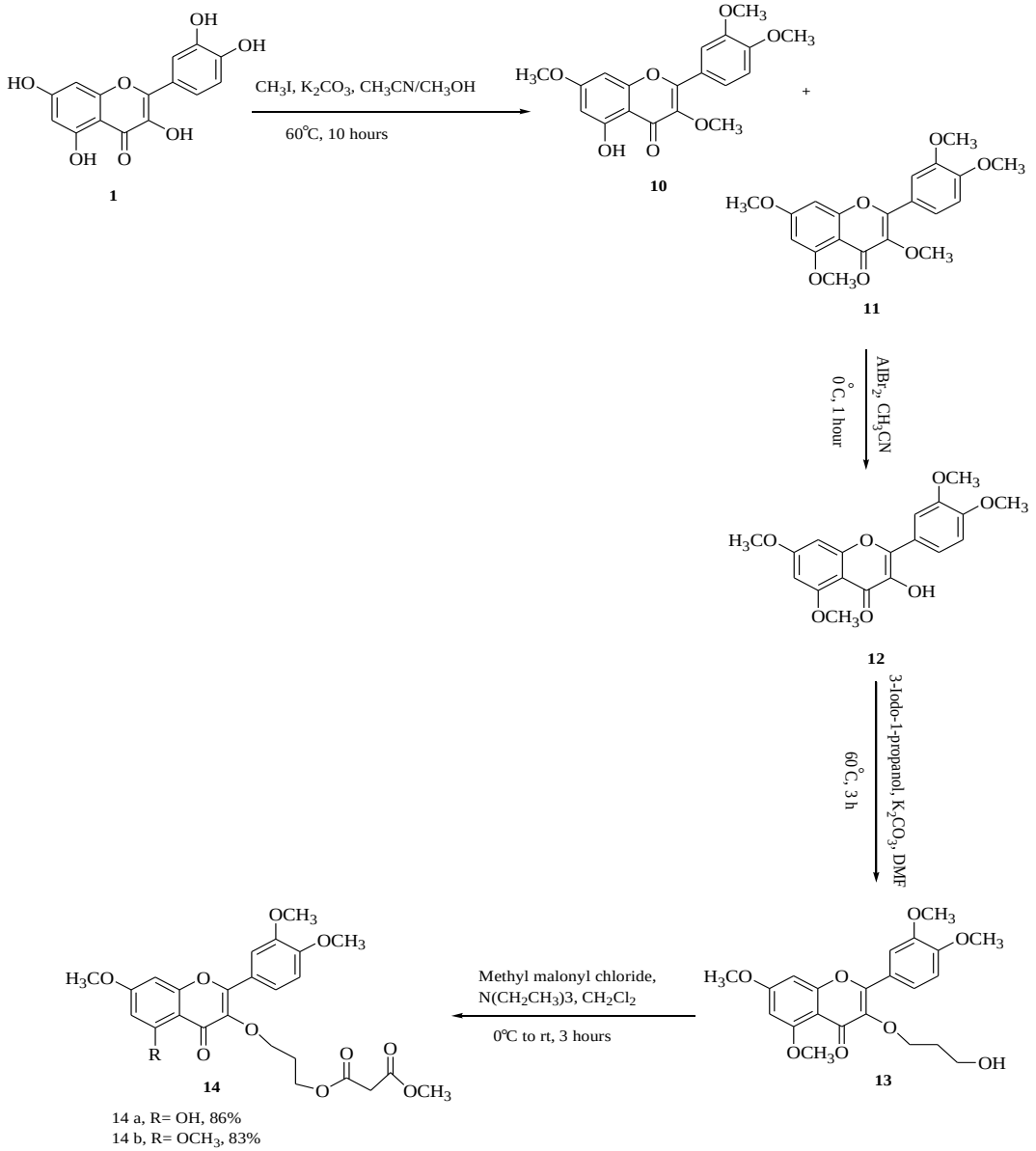
Scheme 1: Synthesis of Tamarixetin

Ravishankar D et al. showed the synthesis of thioquercetin **(9)** by the methylation of **1** was performed with $(CH_3O)_2SO_2$ in the existence of 15 % KOH, which gives methoxy quercetin **(7)** with 60% yield. The product obtained **(7)** was reacted with Lawesson's reagent in dry toluene for four hours at 110 °C, to give thiomethoxyquercetin **(8)**, which was further demethylated by the treatment of BBr_3 in anhydrous CH_2Cl_2 for 18 hours at 40° C, to obtain the final product thioquercetin **(9)** with 55% yield **(Scheme-2)**. **[17]**



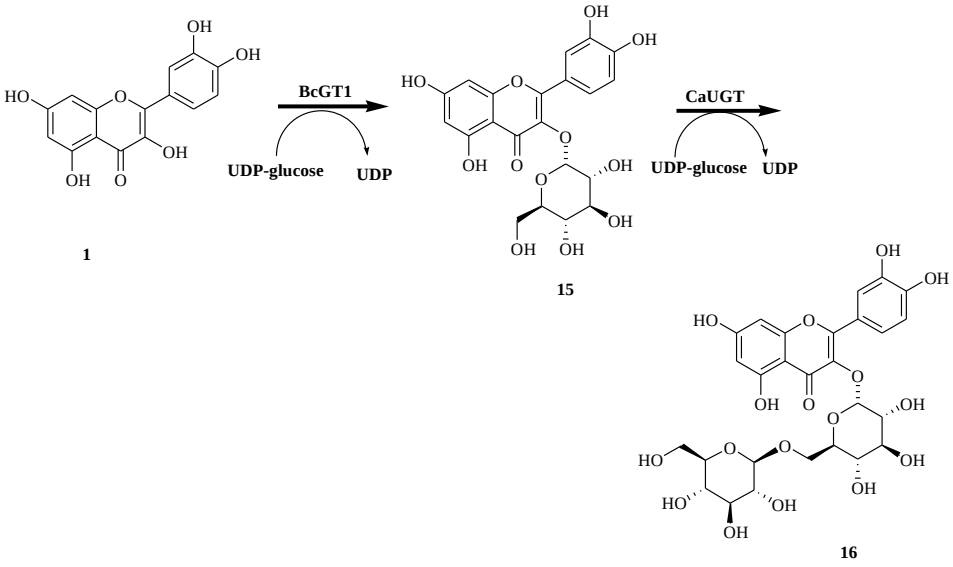
Scheme 2: Synthesis of Thioquercetin

de la Torre et al. reported that when quercetin was methylated using methyl iodide, a combination of molecules **10** and **11** was produced. Compound **11** was demethylated to produce the 3-OH variant **12**. Compound **10** was employed in the process with 3-iodi-1-propanol, and when substance **12** was alkylated with it, it produced the propanol analog **13** immediately in an appropriate ratio. By esterifying those substances with methyl malonyl chloride, the related malonate **14** was obtained at last **[18]**



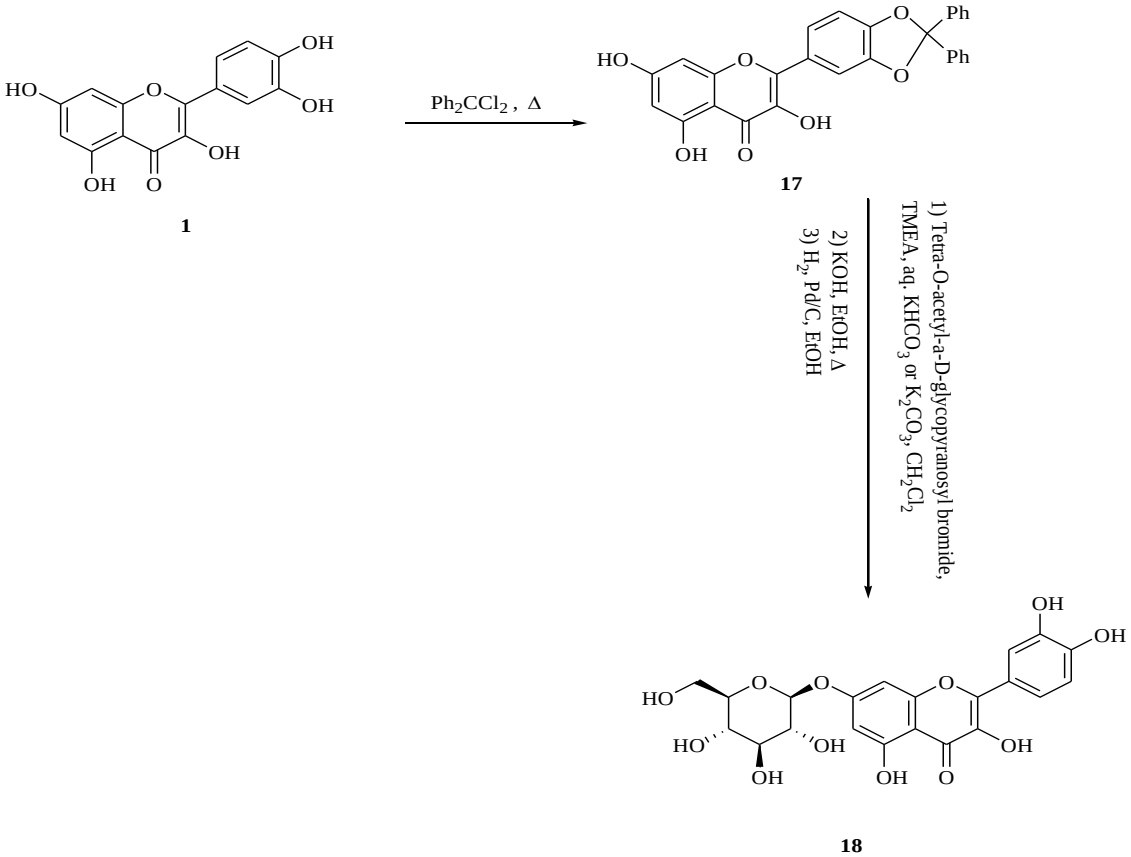
Scheme 3: Synthesis of Malonic acid 3-[2-(3,4-dimethoxy-phenyl) -5,7-dimethoxy-4- oxo-4H- chromen-3-yloxy]-propyl ester methyl ester

Cho A R et.al. obtained quercetin 3-O-gentibioside **(16)** by the two-step reaction of quercetin with BcGT1 which converts quercetin **(1)** into quercetin 3-O-glucoside **(15)**. The second step shows the further synthesis of **(15)** catalyzed by using another glycosyltransferase CaUGT, which synthesizes **16 (Scheme-4)**. Due to the quick transformation of **1** into quercetin 3-O- glucoside, it is essential that BcGT1 be kept at a low concentration **[19]**.



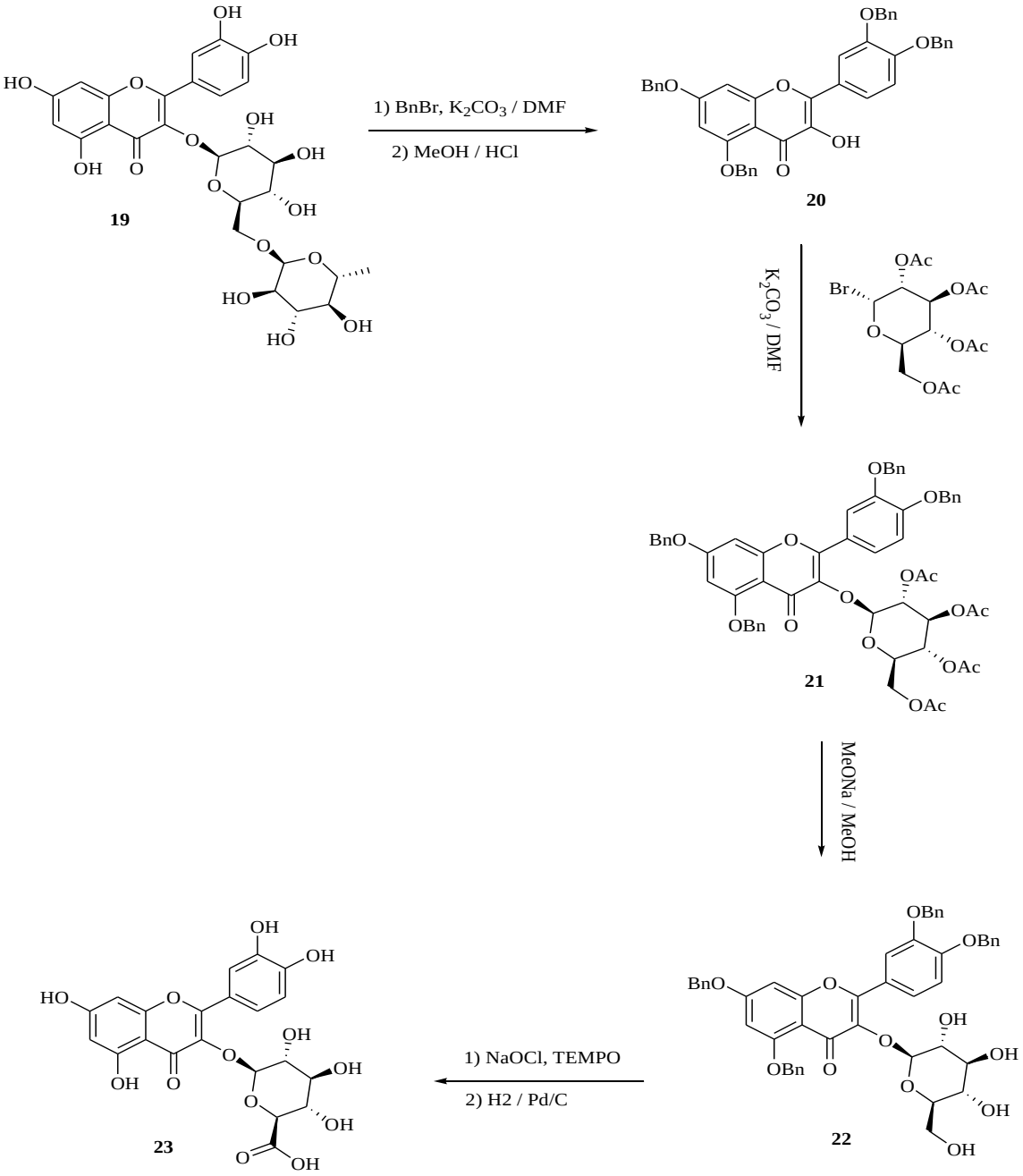
Scheme 4: Synthesis of quercetin 3-O-gentiobioside

Alluis B et al. synthesized 7-O- β- D- glucopyranosylquercetin **(18)** by the immediate heating of **1** with Ph_2CCl_2 at 170° C and transformed it into its diphenyl methylene acetal, which was then used for preparing the methylene acetal. Glycosidation of substance **17** was done under phase-transfer conditions (CH_2Cl_2, saturated $KHCO_3$ mixture, tris [2-(2-methoxy ethoxy) ethyl] (TMEA). Diphenyl methylene acetal was then hydrogenolysis to produce **18 [20].**



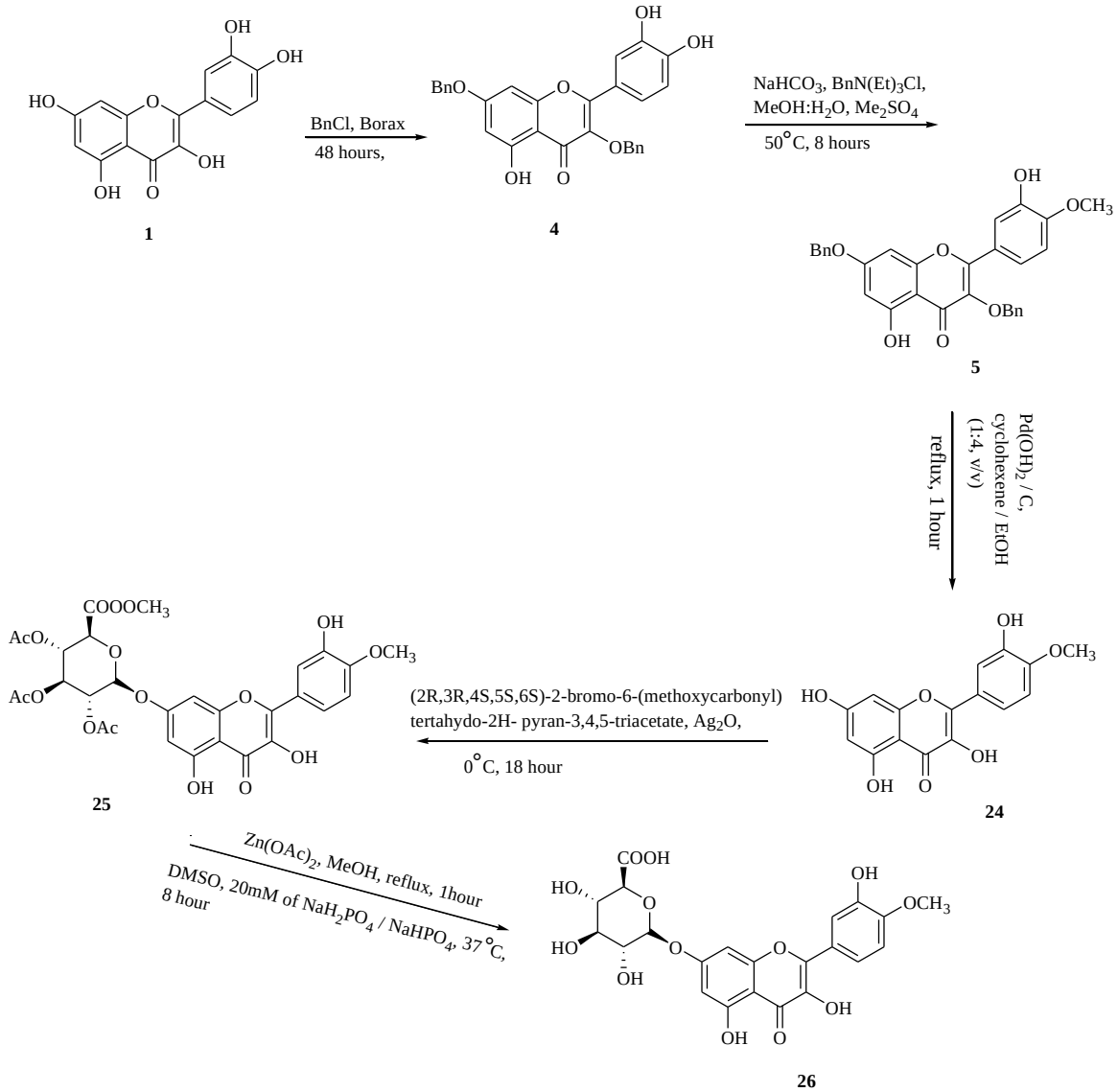
Scheme 5: Synthesis of 7-O-β-d-glucopyranosylquercetin

Kajjout M, et.al., synthesized 3-O- β- D- glucuronide **(23)** by benzylating the four-hydroxyl group of rutin **(19)** with excess BnBr and K_2CO_3 in dimethyl formamide for ten hours at ambient climate. The desired compound 3', 4', 5,7- tetra benzylated quercetin **(20)** was obtained by hydrolyzation of tetra benzylated rutin using a combination solution of methanol/ HCl (98/2, v/v) on reflux at 65° C. By merely employing potassium carbonate as a base and condensing 1-bromo- 3,6,4- tetra-O-acetyl-α-D-glucopyranoside on compound **(20)** in dimethylformamide at the ambient temperature, O-glycosylation was obtained. Oxidation of **(22)** was carried out by sodium hypochlorite (NaCl) which was catalysed by (TEMPO) 2,2,6,6- tetramethyl-1-piperidinyloxy and finished by hydrogenolyzation of benzyl compounds using H_2 / Pd/C. the final product **(23)** was obtained with a 28% yield **[21]**.



Scheme 6: Synthesis of quercetin 3-O-β-D-glucuronide

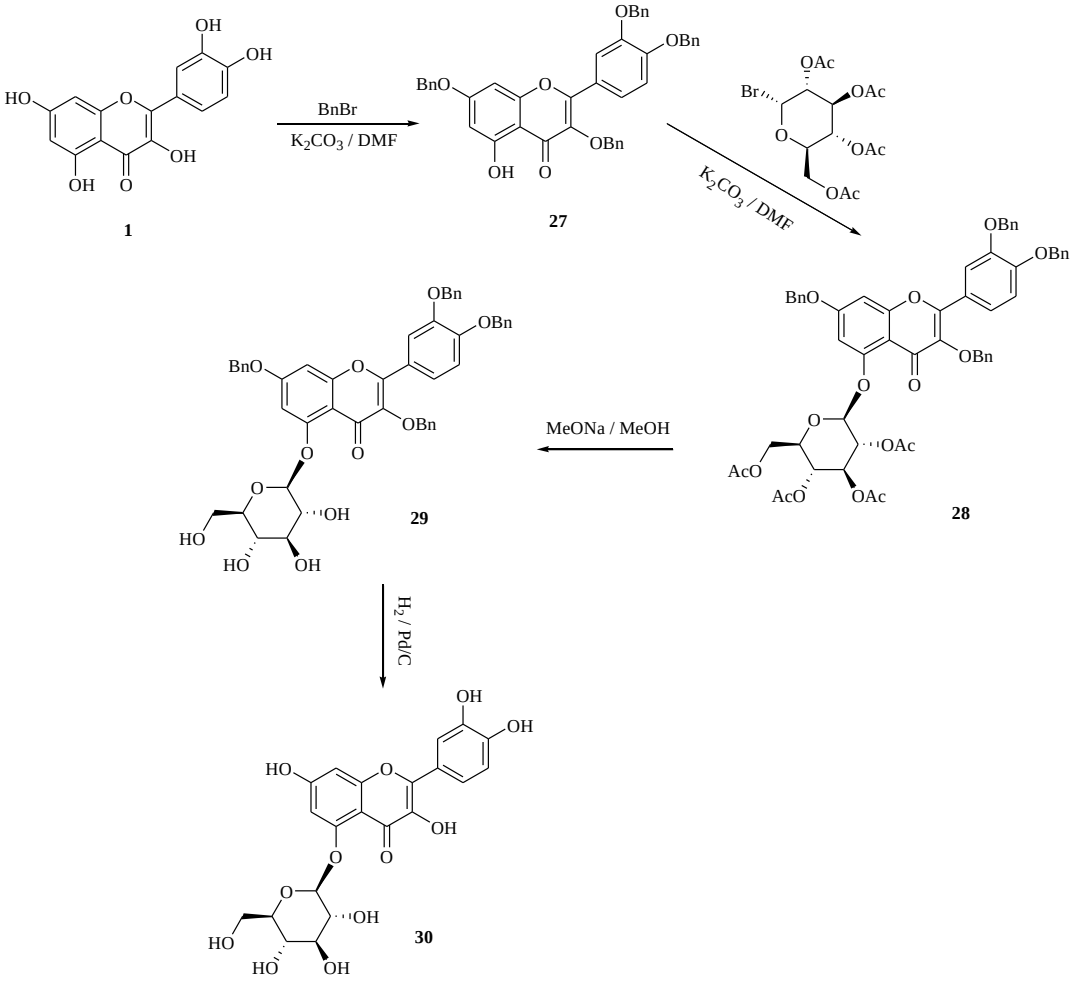
Docampo-Palacios et al. synthesized 4'-O- methyl quercetin-7- O-β- D-glucuronide **(26)** in a six-step process. Borax was used as a chelating substance to protect sites 4' and 3', as well as K_2CO_3, benzyl chloride, and benzyl triethylammonium chloride were used as phase-transfer catalysts, in the production of **4** through benzylating **1**. After that, component **5** was produced by the specific methylation of **4**. Next, the 4'-O-methyl quercetin **(24)** was obtained by debenzylation **5**. Subsequently, the immediate glucuronidation of compound **24** was carried out using the Koenigs-Knorr reaction method. This involves the addition of 2.5 equi. of Ag_2O, and 1.25 equi. of (2R,3R,4S,5S,6S)-2- bromo-6- (methoxycarbonyl) tetrahydro- 2H-pyran-3,4,5-triyltriacetate, resulting in the formation of **26** with 61% yield **[22]**.



Scheme 7: Synthesis of 4′-O- methylquercetin-7-O- β-D- glucuronide

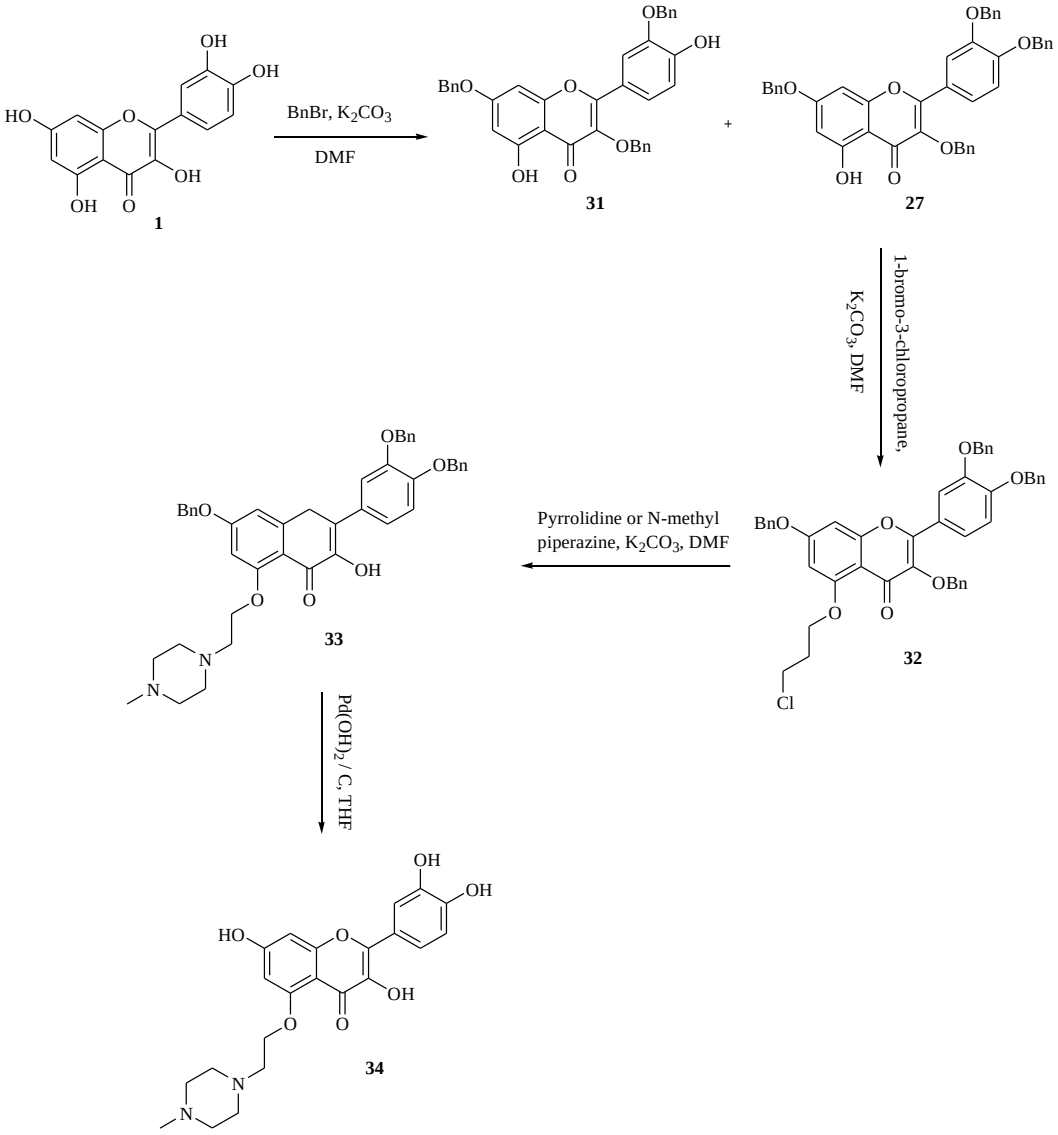
Kajjout M et al. showed the synthesis of quercetin 5-O-β-D-glucoside **(30)** four-step process. Initially, 3,4',3,7-O-tetra benzyl quercetin **(27)** was produced by the benzylation of **1** in DMF at ambient climate with varying concentrations of benzyl bromide and potassium carbonate. Secondly, acetobromoglucose and **27** interact when K_2CO_3 is introduced. Then, under the identical circumstances as previously, the glucoside moiety is deprotected. Thirdly, protected phenolic group **28** is used to

oxidize the primary alcohol of **30**. Lastly, the desired product **30** is obtained by the breakdown of the benzyl ring using H_2, Pd/C giving a 50% yield **[23]**.



Scheme 8: Synthesis of quercetin 5-O-β-D-glucoside

Mukherjee K et al. showed the synthesis of 2-(3,4- Dihydroxyphenyl)- 7,3 -dihydroxy-5-(3-4-methyl piperazine-1-yl)propoxy)-4H- chromen-4- one **(34)** by reacting **1** with BnBr and K_2CO_3 in DMF which was then stirred for 2 hours continuously, which resulted in tri benzyl **31** and tetra benzyl **27**. After that compound **27** was treated with 1-bromo-3-chloropropane and potassium carbonate in DMF and was refluxed for another 6 h, giving product **32**. In compound **32** N-methyl piperazine, DMF, and K_2CO_3 were added which resulted in the formation of **33**, which was further hydrolyzed to obtain the final product **34** with a 73% yield **[24]**



Scheme 9: Synthesis of 2-(3,4- Dihydroxyphenyl)- 7,3 -dihydroxy-5-(3-(4-methyl piperazine-1-yl)propoxy)-4H- chromen-4- one

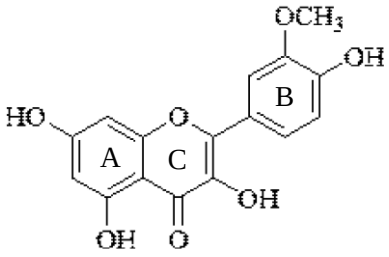
4. BIOLOGICAL ACTIVITIES AND STRUCTURE-ACTIVITY RELATIONSHIP

4.1 Anti-cancer activity

Chan EW. et al. 2021 reported that tamarixetin **(6)** had a cytotoxicity of 19.6 and 20.3 µM, toward tumour cells from the A549 and HCC44 strains, respectively. Compared to quercetin, it had a cytotoxicity that was 3.7 and 5.3 times higher. According to IC50 values, TMT was toxic to four distinct cancer cell types at concentrations of 24 µM for K562 cells, 7.5 µM for Molt-3 cells, 7.5 µM for HL-60 cells, 5.5 µM for U937 cells. TMT illustrated the highest cytotoxic effect when quercetin, 3-O-methyl quercetin, and 7-O-methyl quercetin were evaluated against B16F10 melanoma, C6 glioma, AGS gastric, and HeLa cervical carcinoma cells **[25]**.

Li Q, et al. 2015 stated that **3'-O- methyl quercetin [**isorhamnetin**] (35)** had an impact on A549 cell proliferation as low as 5 µg/ml, and at 320 µg/ml, it had the greatest impact; the IC50 for this action was 44.5 µg/ml. Additionally, they found that compared to other cancer cell lines such as Caco-2, K562, SMMC7721, PC3, MCF-7, and others,

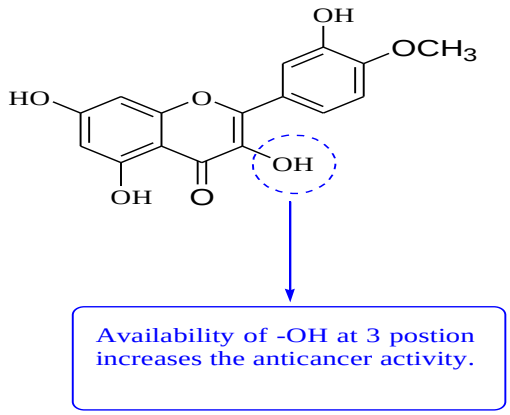
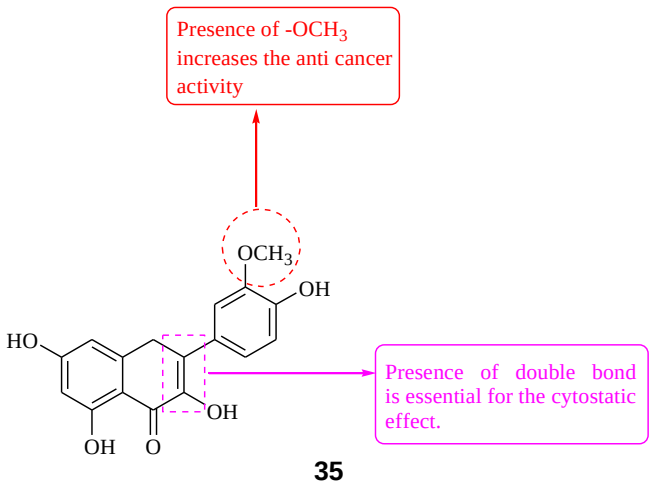
lung cell line A549 had a larger effect on growth inhibition. The IC50 for isorhamnetin varied between 57.2 µg/ml to 129.1 µg/ml. It exhibits potent anticancer properties *in vivo* **[26]**. The cell death signals composed of caspase-3, p53, and Bax are activated by isorhamnetin in cancerous cells, which stops them from proliferating **[27]**.



35

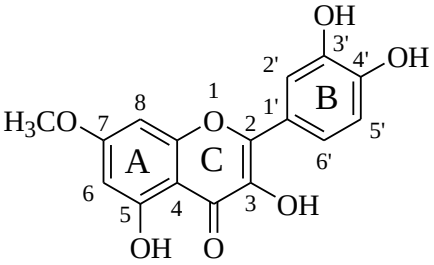
Xu D, et al. 2019 found that prostate, lung, liver, colon, cervical tumor, and breast are just a few of the many malignancies that can be stopped from spreading by using **quercetin**. Its anti-cancer properties are accomplished by several methods including cell communication channels and enzymatic reactions that prevent carcinogenesis. The most frequent deactivated tumor suppressor, p53, is stimulated by quercetin to inhibit the growth of cancer **[28]**.

Table 1: SAR of anti-cancer quercetin derivative [29,30]

S.No.	SAR
1.	 **6**
2.	 **35**

4.2 Anti-tubercular activity

Kim MJ, et al. 2016 reported **Rhamnetin's (36)** anti-tubercular activity in opposition to extensively drug-resistant (XDR) strains, *Mycobacterium tuberculosis* $H_{37}RV$, and multi-drug-resistant (MDR). Having an MIC_{90} value of 100 µg/ml, rhamnetin prevented the expansion of the $H_{37}Rv$ bacterium. MDR strains had an MIC_{90} of 200 whereas XDR isolates had an MIC_{90} of 100 µg/ml correspondingly **[31]**.



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Sasikumar K et. al 2018 stated that the strand of DNA gyrase unit B in *M. Tuberculosis* is blocked by **quercetin (1)**. In addition, it blocks the production of mycolic acid by the enzyme beta-ketoacyl ACP synthase III. Additionally, it was also noted that it has an IC50 of 71.30µM and blocks 75% of *Mycobacteria proteasomes* **[32]**.

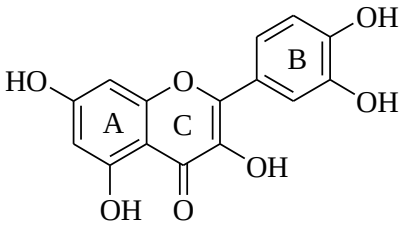

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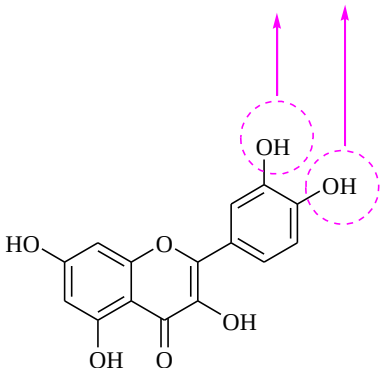
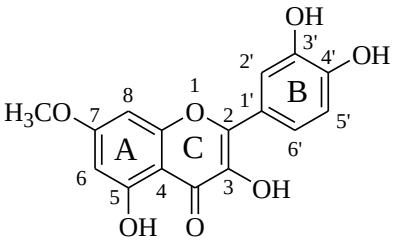
Table 2: SAR of Anti-tubercular Activity [33]

S.No.	SAR
1.	Presence of -OH inhibit the tuberclosis activity.  **1**

4.3 Anti-inflammatory activity

Nitric oxide (NO), an unstable substance that is essential for cell growth and survival, has a variety of inflammatory agent impacts on a wide range of different kinds of cells. **Jnawali HN et. al 2014** observed the aggregation of nitrite in the growing medium, and it was possible to determine the consequences of various amounts of **rhamnetin** (1, 2.5, 5, 10, and 20 µM) on lipopolysaccharide (LPS) -induced NO generation in RAW264.7 cells. The nitric oxide amount was elevated by the LPS. The concentration of nitric oxide produced by LPS was reduced by 62% and 74%, correspondingly, when treated with 10 and 20µM rhamnetin **[34]**. Rhamnetin inhibits NO formation and proves its inhibition property is far superior than other flavonols **[35]**.



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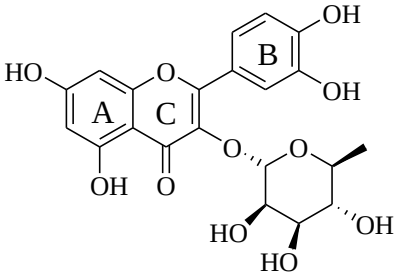
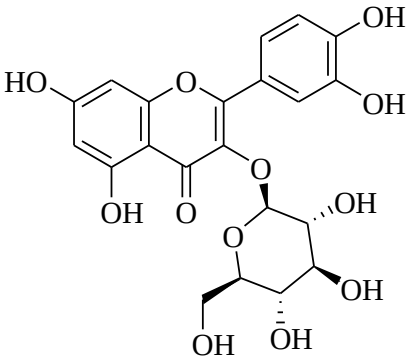
Quercitrin (38), a member of the flavonoid family, reduced TNF-α, which is included in the inflammation process. According to **Ginting CN *et al., 2019*** quercitrin works to reduce inflammation by preventing the body's natural synthesis of the proinflammatory cytokine TNF-α and it elevates IL-10 cytokine that also reduces inflammatory cytokines **[36]**.



38

High mobility group box 1 (HMGB1) is an inherent DAMPs enzyme which trigger the pro inflammatory transmission cascade, aggravating the destruction of tissues and organs **[37]**. **Valentová K et al., 2014** observed that by reducing the action of cyclooxygenase-2, **isoquercitrin (39)** might reduce the amount of prostaglandin E2 generated by LPS-stimulated RAW264.7 cells **[38]**.

Shen Y et al., 2020 discovered that denervated target muscles had greatly elevated production levels of inflammatory protein and gene expression (IL-6, TNF-α, and IL-1β). The inflammatory mediators (IL-6, TNF-α, and IL-1β) were considerably reduced by isoquercitrin therapy in denervated target muscles. Compared to QUR, isoquercitrine exhibits a significantly wider range of medicinal properties and is significantly more effective. **[39]**.



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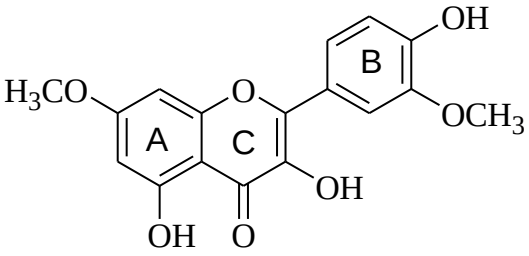
4.4 Antibacterial activity

Martini ND *et al. 2004* found that the greatest efficacy was shown against the *Enterococcus faecalis* (50 µg/ml) along with *Vibrio cholerae* (25-50 µg/ml) which was prohibited by **Rhamnazin (40)**. And around 50-100 µg/ml *Pseudomonas aeruginosa* and *Escherichia coli* were found to be inhibited. It also hinders the development of *Staphylococcus aureus* having a MIC value of 50 µg/ml **[40]**.



41

Restoration of tissue or bodily equilibrium involves inflammation, a crucial biological reaction. But high levels of inflammation may result in unneeded collateral damage and have damaging implications **[41]**. **Wang L, et al., (2013)** found that the MIC (minimum inhibition concentration) of **isoquercetin (42)** P. acnes, S. epidermidis, P. acnes, and S. aureus were 2048, 512, 1024, and 2048 µg/ml respectively. Four-test strain development can also be inhibited by isoquercetin but has no bactericidal activity **[42]**.

5. CONCLUSION

In this paper, numerous methodologies for the synthesis of quercetin variants are presented, with a focus on recently reported chemical procedures for quercetin-containing substances together with a pharmacological effect and structure-activity relationship. A connection between multiple derivatives comprising quercetin and the function group was discovered in the section that focuses on the structural-activity relationship.

According to the majority of the published studies, the quercetin component is crucial for the therapeutic properties of substances that have a variety of physiological effects, including those that are anti-tubercular, anti-cancer, antimicrobial, anticonvulsant, and anti-inflammation. We anticipate that this paper will give researchers who are working with quercetin in any capacity the vital most recent knowledge.

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References

1) Yang D, Wang T, Long M, Li P. Quercetin: its main pharmacological activity and potential application in clinical medicine. Oxidative Medicine and Cellular Longevity. 2020 Oct;2020.

2) Nassiri-Asl M, Hajiali F, Taghiloo M, Abbasi E, Mohseni F, Yousefi F. Comparison between the effects of quercetin on seizure threshold in acute and chronic seizure models. Toxicology and industrial health. 2016 May;32(5):936-44.

3) Vazhappilly CG, Amararathna M, Cyril AC, Linger R, Matar R, Merheb M, Ramadan WS, Radhakrishnan R, Rupasinghe HV. Current methodologies to refine bioavailability, delivery, and therapeutic efficacy of plant flavonoids in cancer treatment. The Journal of Nutritional Biochemistry. 2021 Aug 1;94:108623.

4) Duan Y, Sun N, Xue M, Wang X, Yang H. Synthesis of regioselectively acylated quercetin analogues with improved antiplatelet activity. Molecular Medicine Reports. 2017 Dec 1;16(6):9735-40.

5) Rauf A, Imran M, Khan IA, ur-Rehman M, Gilani SA, Mehmood Z, Mubarak MS. Anticancer potential of quercetin: A comprehensive review. Phytotherapy Research. 2018 Nov;32(11):2109-30.

6) Lesjak M, Beara I, Simin N, Pintać D, Majkić T, Bekvalac K, Orčić D, Mimica-Dukić N. Antioxidant and anti-inflammatory activities of quercetin and its derivatives. Journal of Functional Foods. 2018 Jan 1;40:68-75.

7) Xu D, Hu MJ, Wang YQ, Cui YL. Antioxidant activities of quercetin and its complexes for medicinal application. Molecules. 2019 Mar 21;24(6):1123.

8) Miltonprabu S, Tomczyk M, Skalicka-Woźniak K, Rastrelli L, Daglia M, Nabavi SF, Alavian SM, Nabavi SM. Hepatoprotective effect of quercetin: From chemistry to medicine. Food and Chemical Toxicology. 2017 Oct 1;108:365-74.

9) Elbarbry F, Abdelkawy K, Moshirian N, Abdel-Megied AM. The antihypertensive effect of quercetin in young spontaneously hypertensive rats; role of arachidonic acid metabolism. International Journal of Molecular Sciences. 2020 Sep 8;21(18):6554.

10) Kim CH, Kim JE, Song YJ. Antiviral activities of quercetin and isoquercitrin against human herpesviruses. Molecules. 2020 May 20;25(10):2379.

11) Pawar A, Jha P, Chopra M, Chaudhry U, Saluja D. Screening of natural compounds that targets glutamate racemase of Mycobacterium tuberculosis reveals the anti-tubercular potential of flavonoids. Scientific reports. 2020 Jan 22;10(1):949.

12) Parihar G, Dehariya B, Ghule S, Dixit P, Balekar N. Quercetin exerts anti-convulsant effects in animal model of grand mal epilepsy: Modulation of GABA and glycinergic pathways. Journal of Drug Delivery and Therapeutics. 2017 Dec 22;7(7):194-6.

13) Nguyen TL, Bhattacharya D. Antimicrobial activity of quercetin: an approach to its mechanistic principle. Molecules. 2022 Apr 12;27(8):2494.

14) Ozgen S, Kilinc OK, Selamoğlu Z. Antioxidant activity of quercetin: a mechanistic review. Turkish Journal of Agriculture-Food Science and Technology. 2016 Dec 18;4(12):1134-8.

15) Musarra-Pizzo M, Pennisi R, Ben-Amor I, Mandalari G, Sciortino MT. Antiviral activity exerted by natural products against human viruses. Viruses. 2021 May 4;13(5):828.

16) Hirpara KV, Aggarwal P, Mukherjee AJ, Joshi N, Burman AC. Quercetin and its derivatives: synthesis, pharmacological uses with special emphasis on anti-tumor properties and prodrug with

enhanced bio-availability. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2009 Feb 1;9(2):138-61.

17) Ravishankar D, Watson KA, Boateng SY, Green RJ, Greco F, Osborn HM. Exploring quercetin and luteolin derivatives as antiangiogenic agents. European journal of medicinal chemistry. 2015 Jun 5;97:259-74.

18) de la Torre MD, Tomé AC, Silva AM, Cavaleiro JA. Synthesis of [60] fullerene–quercetin dyads. Tetrahedron letters. 2002 May 28;43(26):4617-20.

19) Cho AR, An DG, Lee Y, Ahn JH. Biotransformation of quercetin to quercetin 3-O-gentiobioside using engineered Escherichia coli. Applied Biological Chemistry. 2016 Oct;59:689-93.

20) Alluis B, Dangles O. Quercetin (= 2-(3, 4-Dihydroxyphenyl)-3, 5, 7-trihydroxy-4H-1-benzopyran-4-one) glycosides and sulfates: chemical synthesis, complexation, and antioxidant properties. Helvetica Chimica Acta. 2001 May 16;84(5):1133-56.

21) Kajjout M, Zemmouri R, Rolando C. An expeditious synthesis of quercetin 3-O-β-d-glucuronide from rutin. Tetrahedron letters. 2011 Sep 14;52(37):4738-40.

22) Docampo-Palacios ML, Alvarez-Hernández A, Adiji O, Gamiotea-Turro D, Valerino-Diaz AB, Viegas LP, Ndukwe IE, De Fátima Â, Heiss C, Azadi P, Pasinetti GM. Glucuronidation of methylated quercetin derivatives: chemical and biochemical approaches. Journal of agricultural and food chemistry. 2020 Dec 8;68(50):14790-807.

23) Kajjout M, Rolando C. Regiospecific synthesis of quercetin O-β-d-glucosylated and O-β-d-glucuronidated isomers. Tetrahedron. 2011 Jun 24;67(25):4731-41.

24) Mukherjee A, Mishra S, Kotla NK, Manna K, Roy S, Kundu B, Bhattacharya D, Das Saha K, Talukdar A. Semisynthetic quercetin derivatives with potent antitumor activity in colon carcinoma. Acs Omega. 2019 Apr 22;4(4):7285-98.

25) Chan EW, Ng YK, Tan CY, Alessandro L, Wong SK, Chan HT. Diosmetin and tamarixetin (methylated flavonoids): A review on their chemistry, sources, pharmacology, and anticancer properties. Journal of Applied Pharmaceutical Science. 2021 Feb 10;11(3):022-8.

26) Li Q, Ren FQ, Yang CL, Zhou LM, Liu YY, Xiao J, Zhu L, Wang ZG. Anti-proliferation effects of isorhamnetin on lung cancer cells in vitro and in vivo. Asian Pacific Journal of Cancer Prevention. 2015;16(7):3035-42.

27) Seo S, Seo K, Ki SH, Shin SM. Isorhamnetin inhibits reactive oxygen species-dependent hypoxia inducible factor (HIF)-1α accumulation. Biological and Pharmaceutical Bulletin. 2016 Nov 1;39(11):1830-8.

28) Xu D, Hu MJ, Wang YQ, Cui YL. Antioxidant activities of quercetin and its complexes for medicinal application. Molecules. 2019 Mar 21;24(6):1123.

29) Chen L, Teng H, Xie Z, Cao H, Cheang WS, Skalicka-Woniak K, Georgiev MI, Xiao J. Modifications of dietary flavonoids towards improved bioactivity: An update on structure–activity relationship. Critical reviews in food science and nutrition. 2018 Mar 4;58(4):513-27.

30) Menezes JC, Orlikova B, Morceau F, Diederich M. Natural and synthetic flavonoids: structure–activity relationship and chemotherapeutic potential for the treatment of leukemia. Critical reviews in food science and nutrition. 2016 Jul 29;56(sup1):S4-28.

31) Kim MJ, Jeon D, Kwak C, Ryoo S, Kim Y. Rhamnetin Exhibits Anti-Tuberculosis Activity and Protects against Lung Inflammation. Bulletin of the Korean Chemical Society. 2016 Oct;37(10):1703-9.

32) Sasikumar K, Ghosh AR, Dusthackeer A. Antimycobacterial potentials of quercetin and rutin against Mycobacterium tuberculosis H37Rv. 3 Biotech. 2018 Oct;8:1-6.

33) Jnawali HN, Jeon D, Jeong MC, Lee E, Jin B, Ryoo S, Yoo J, Jung ID, Lee SJ, Park YM, Kim Y. Antituberculosis activity of a naturally occurring flavonoid, isorhamnetin. Journal of natural products. 2016 Apr 22;79(4):961-9.

34) Jnawali HN, Lee E, Jeong KW, Shin A, Heo YS, Kim Y. Anti-inflammatory activity of rhamnetin and a model of its binding to c-Jun NH2-terminal kinase 1 and p38 MAPK. Journal of natural products. 2014 Feb 28;77(2):258-63.

35) Lee H, Krishnan M, Kim M, Yoon YK, Kim Y. Rhamnetin, a Natural Flavonoid, Ameliorates Organ Damage in a Mouse Model of Carbapenem-Resistant Acinetobacter baumannii-Induced Sepsis. International Journal of Molecular Sciences. 2022 Oct 25;23(21):12895.

36) Ginting CN, Lister IN, Girsang E, Mutia MS, Lubis YE, Amalia A, Rizal R, Widowati W. Anti-inflammatory Activity of Quercitrin on Hypoxia-induced EA. hy926. InJournal of Physics: Conference Series 2019 Nov 1 (Vol. 1374, No. 1, p. 012033). IOP Publishing.

37) Shen P, Peng Y, Zhou X, Jiang X, Raj R, Ge H, Wang W, Yu B, Zhang J. A comprehensive spectral and in silico analysis on the interactions between quercetin, isoquercitrin, rutin and HMGB1. LWT. 2022 Nov 1;169:113983.

38) Valentová K, Vrba J, Bancířová M, Ulrichová J, Křen V. Isoquercitrin: Pharmacology, toxicology, and metabolism. Food and Chemical Toxicology. 2014 Jun 1;68:267-82.

39) Shen Y, Zhang Q, Huang Z, Zhu J, Qiu J, Ma W, Yang X, Ding F, Sun H. Isoquercitrin delays denervated soleus muscle atrophy by inhibiting oxidative stress and inflammation. Frontiers in physiology. 2020 Aug 12;11:988.

40) Martini ND, Katerere DR, Eloff JN. Biological activity of five antibacterial flavonoids from Combretum erythrophyllum (Combretaceae). Journal of ethnopharmacology. 2004 Aug 1;93(2-3):207-12.

41) Choi SS, Park HR, Lee KA. A comparative study of rutin and rutin glycoside: antioxidant activity, anti-inflammatory effect, effect on platelet aggregation and blood coagulation. Antioxidants. 2021 Oct 27;10(11):1696.

42) Wang L, Yang X, Qin P, Shan F, Ren G. Flavonoid composition, antibacterial and antioxidant properties of tartary buckwheat bran extract. Industrial Crops and Products. 2013 Aug 1;49:312-7.