Sys Rev Pharm 2020; 11(4): 175 – 187
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Antitumor, Antioxidant, and Antibacterial Activities of Glycosyl-Conjugated Compounds: A Review

Moath Kahtan Bashir[1], Yasser Fakri Mustafa[2*], Mahmood Khudhayer Oglah[3]
[1,2,3]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.
Corresponding Author mail id: Dr.yassermustafa@uomosul.edu.iq

Article History: *Submitted: 24.01.2020* *Revised: 20.03.2020* *Accepted: 11.04.2020*

ABSTRACT
There is a developing interest for the utilization of glycosyl-conjugation to improve the biological and pharmacokinetic properties of different medicinally active products. This is manifested by the presence of a significant number of research papers concerning the boosting of various therapeutic potentials of known drugs by their conjugation with different mono-, di-, or poly-saccharides. This review summarizes the most important and most recent examples of this conjugation, especially those related to the enhancement of antitumor, antioxidant and antibacterial activities of the original drugs. These examples with the proposed mechanisms of activity improvement may guide to design, synthesis and evaluation of new glycosyl-conjugates for better therapeutics.

Keywords: Glycosylation, Antitumor, Antioxidant, Antibacterial.

Correspondence:
Yasser Fakri Mustafa
Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq
E-mail: Dr.yassermustafa@uomosul.edu.iq

DOI: 10.31838/srp.2020.4.26

INTRODUCTION

In biology, the glycosylation is an important and essential enzymatic process through which glycones are attached to proteins, lipids, or other biological molecules. Evidence showed that the majority of proteins in eukaryotes are post-translationally glycosylated in the plasma membrane, endoplasmic reticulum, and Golgi apparatus. Such glycosylation plays an important role in the protein stability, cell adhesion, cellular interaction, protein folding, and even in signal transduction. Hence, any defect in the glycosylation process was found to be related to many metabolic, neurodegenerative, and neoplastic disorders [1].

The glycosidic linkages in different glycoproteins are classified according to the functional part of amino acid which conjugates with the sugar. In living organisms, there are 37 types of glycoprotein linkages have been detected, in which thirteen different monosaccharides and eight amino acids are involved. The well-known classes include S-linked, N-linked, P-linked, C-linked, and O-linked glycoproteins. Among them, the O- and N-linked glycoproteins are the most common [2].

The hydroxyl moiety of serine, threonine, hydroxylysine, and hydroxyproline can interact with monosaccharide affording O-linked glycoproteins. Asparagine is the most common amino acid contributed to the formation of N-linked glycoproteins, while P-linked glycoproteins are generated when the phosphorylated serine linked to monosaccharide. Also, cysteine is the major amino acid which participates in the formation of S-linked glycoproteins, while C-linked glycoproteins are generated as tryptophan grafted to monosaccharide. Glypiation is an another glycoprotein class which occurs when glycophosphatidylinositol (GPI) glycolipid attached to the C-terminus of a protein [3].

In general, glycoproteins are highly found in the cell membrane of eukaryotes. These proteins play important cellular roles due to their participation in the cell-cell recognition and binding to other molecules, beside their role in the intracellular communications [4].

In 1920s, the German scientist Otto Warburg found that the cancerous tissues have a high rate of aerobic glycolysis and their energy is mainly captured from glycolysis rather than mitochondrial oxidative phosphorylation. Hence, these tissues consume a larger amount of glucose compared to the normal tissues. This phenomenon has been commonly known as a Warburg effect and considered as one of the most important indicators of the cancer evolution [5,6].

Laterally, Warburg proposed that the mitochondrial dysfunction is the fundamental cause for enhancing aerobic glycolysis in cancerous tissue. Normally, this type of glycolysis can generate about 17% of the total ATP molecules needed to fulfill the cellular functions. Since cancer cells need more energy for their rapid multiplication [7], over-expression of insulin independent glucose gated channels (GLUT-1) [8] and induction of glycolytic enzymes [9] are the most acceptable mechanisms to satisfy this energy requirement.

The higher glucose consumption of cancer cells was used as a marker for the existence of cancerous tissues and also for the assessment of patient response to the treatment. This marker is verified by identifying the foundation of a radiolabel glucose analogue termed ^{18}F-FDG in cancer tissue using the positron emission tomography [10]. For the healthy individual, this analogue can be uptaken by only tissues with the highest ability of consuming glucose including brain and bladder. For the patient enduring from cancer, this glucose analogue is selectively concentrated in the cancer cells besides its uptaken by the high glucose-consuming tissues. This is mainly attributed to the over expression of GLUT-1 [11].

Regarding the antibacterial activity of glycosyl-conjugates, the attention has been directed in the last three decades toward the antibacterial agents grafted to different types of simple sugars. The main goals of this approach are to reduce the bacterial resistance and to improve the antibacterial activity [12]. Also, the antiradical capacity of many natural and synthetic antioxidants have been document to be improved through their conjugation with different types of simple sugars. This is may be due to the improvement of aglycones' diffusion into intestinal enterocytes and the chemical stability of the resultant conjugates [13].

This review focused on the progress and future directions of exploiting the Warburg effect for selective targeting the antitumor agents to cancer cells. Also the role of

glycosylation in the improvement of antibacterial and antioxidant activities of their aglycones.

Glycosylation is a new trend for improving the antitumor activity

In the early of 1990s, the idea of grafting mono, di, or polysaccharide to various cytotoxic agents through O-, N-, C- or S-glycosidic linkage has been established. The resultant conjugates showed an improved water solubility, serum stability, and better targeting of their aglycones to the cancerous tissues [14-18].

O-glycosylation for enhancing the aglycone cytotoxic activity

Pohl *et al* have developed glufosfamide (Figure 1), which is a glycosylated ifosfamide, in an effort to increase the selectivity and reduce the toxicity of the original cytotoxic drug. The results showed an increase in the survival time of test animals received glufosfamide with LD_{50} greater by 4.5 times for rats and by 2.3 times for mice than those of ifosfamide [19].

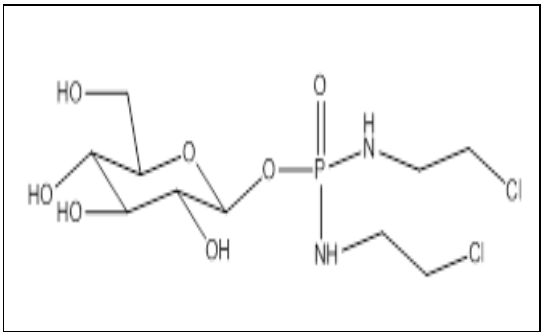

Figure 1: Chemical structure of glufosfamide.

In 1997, Briasoulis *et al* have started the human clinical trials on glufosfamide on twenty patients with tumors of various origins. The maximum tolerated dose was determined to be 190 mg/kg, which is much less than that of ifosfamide (530 mg/kg); consequently, the toxic side effects of glufosfamide was reduced compared with the free aglycone. In this study, ten patients lived with a stable disease, two patients experienced a good response with one of them had complete remission for more than four years, while the remaining eight patients have suffered from a progression of their disease conditions [20].

In order to improve the cytotoxic activity and reduce the toxic side effects of taxoids, Mandai *et al* were linked paclitaxel at positions 7 and 10 with different monosaccharides including galactose, mannose, glucose, and xylose (Figure 2). The results showed that the resulted four glycosyl- conjugates from the linking at position 10 have more water solubility and better cytotoxic activity than those of non-glycosylated compound [21].

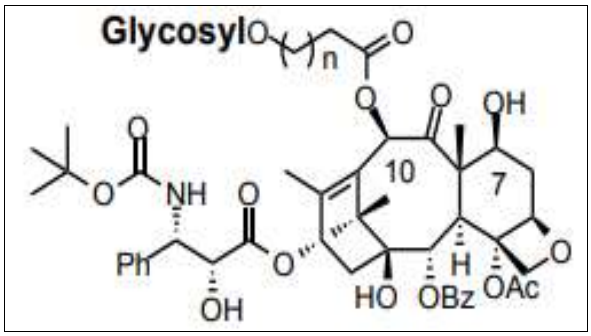

Figure 2: The general chemical structure of the glycosylated paclitaxel conjugates which have an improved antitumor potential.

Lin *et al* have synthesized four novel paclitaxel based glycosyl-conjugates through an ester or ether linkage at the 2' position of paclitaxel. The results revealed that compound shown in Figure 3 with an ester linkage has the best cytotoxic activity and the least side effects [22].

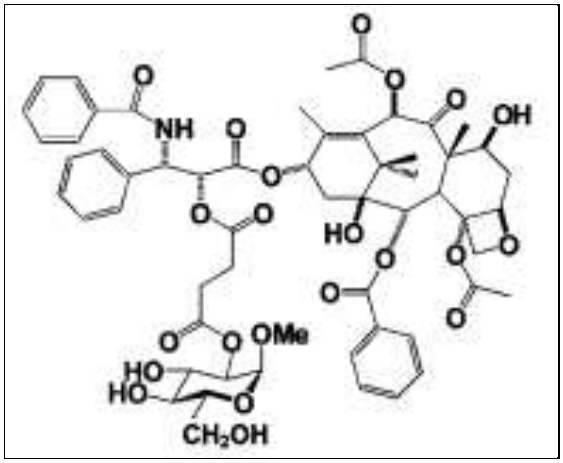

Figure 3: Chemical structure of the glycosylated paclitaxel which prepared by Lin *et al*.

Podophyllotoxin is a natural aryltetralin lignin isolated from the root of the plant *Podophyllum peltatum*. This natural product possess a good cytotoxic activity versus different cancer cell lines acting on colchicine-binding site on tubulin. The high toxicity and poor water solubility are the main obstacles of podophyllotoxin utilization as an anticancer drug. Many efforts have been made to overcome these issues such as the synthesis of per-butyrylated glucoside and 4β-triazolyl-podophyllotoxin glucoside. The compound shown in Figure 4 revealed the highest cytotoxic activity versus five different cancer cell lines with IC_{50} ranging from 3.27 ± 0.21 to 11.37 ± 0.52 µM [23].

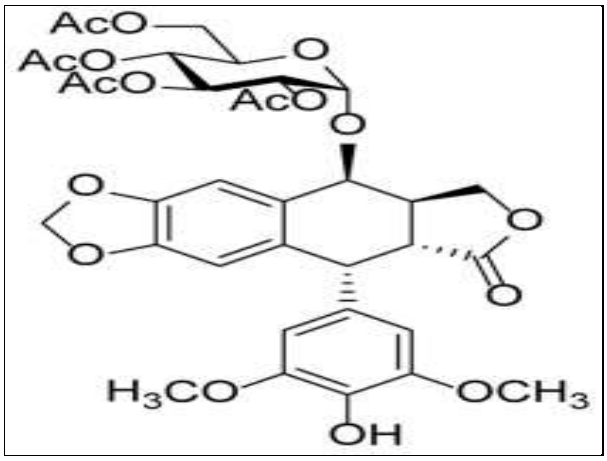

Figure 4: Chemical structure of glycosylated podophyllotoxin which showed an improved cytotoxic activity.

Platinum (IV) prodrugs are used for the treatment of many tumor kinds such as ovarian, head, lung, neck, and colorectal cancers. These prodrugs are usually activated through intracellular reduction followed the cellular uptake. Depending on Warburg phenomena, Ma *et al* synthesized a series of glycosylated platinum (IV) prodrugs in order to improve their chemical stability and tumor selectivity. The results exhibited that the compounds shown in Figure 5 have a higher cytotoxic activity for about 166 folds than cisplatin (Figure 6, a), oxaliplatin (Figure 6, b), and satraplatin (Figure 6, c) [24].

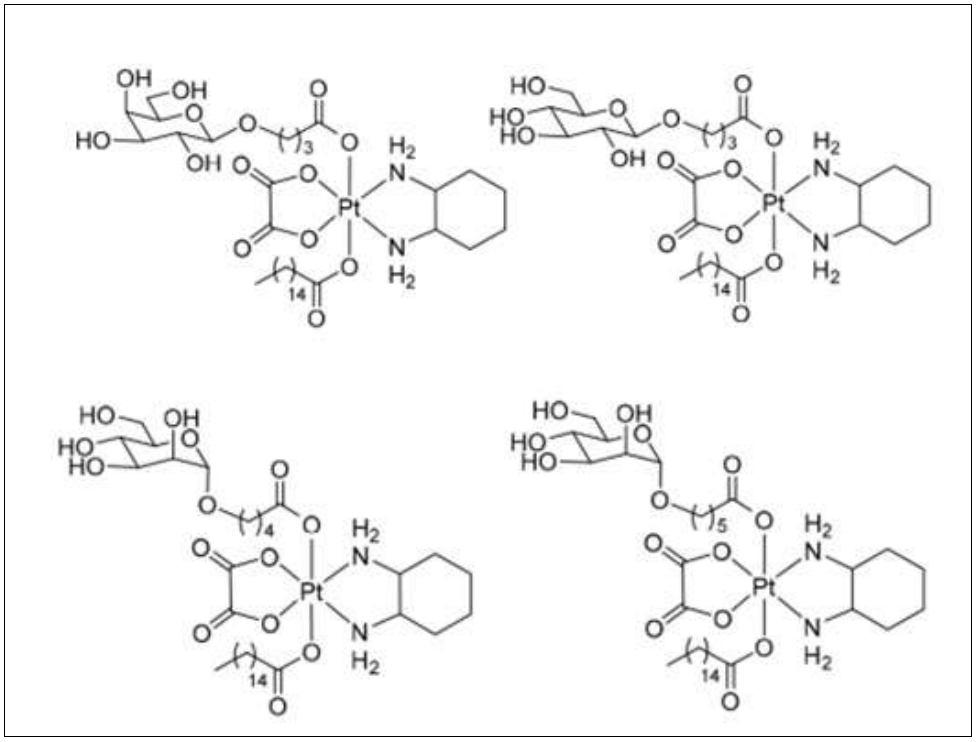

Figure 5: Chemical structures of glycosylated platinum (IV) prodrugs with improved chemical stability and tumor selectivity.

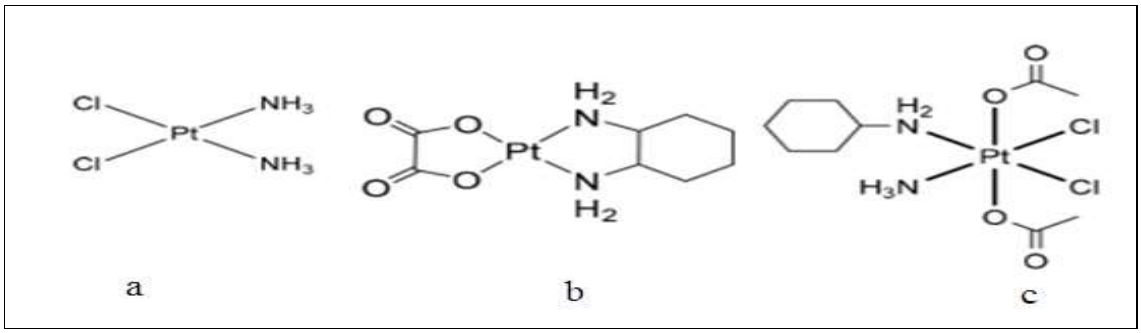

Figure 6: Chemical structures of well-known platinum (IV) prodrugs.

Glycosylatd Antitumor Ether Lipids (GAELs) are synthetic antitumor agents which possess an inhibitory cytotoxic activity on cancer stem cells responsible for tumor relapse. The 2-amino-2-deoxy-D-gluco-based GAELs such as α-GLN (Figure 7, a) and β-GLN (Figure 7, b) showed an improved antitumor activity against epithelial cancer cells in addition to their stem cells. This action, which may be attributed to the presence of amine group in the sugar part, was hypothesized to be due to the generation of acidic vacuoles that release acid and induces cell death. This hypothesis has been augmented by the synthesis of bisamino GAEL compounds (Figure 7, c-e) which possessed 2-3 folds activity against the test cancer cell lines and their stem cells compared to β-GLN [25].

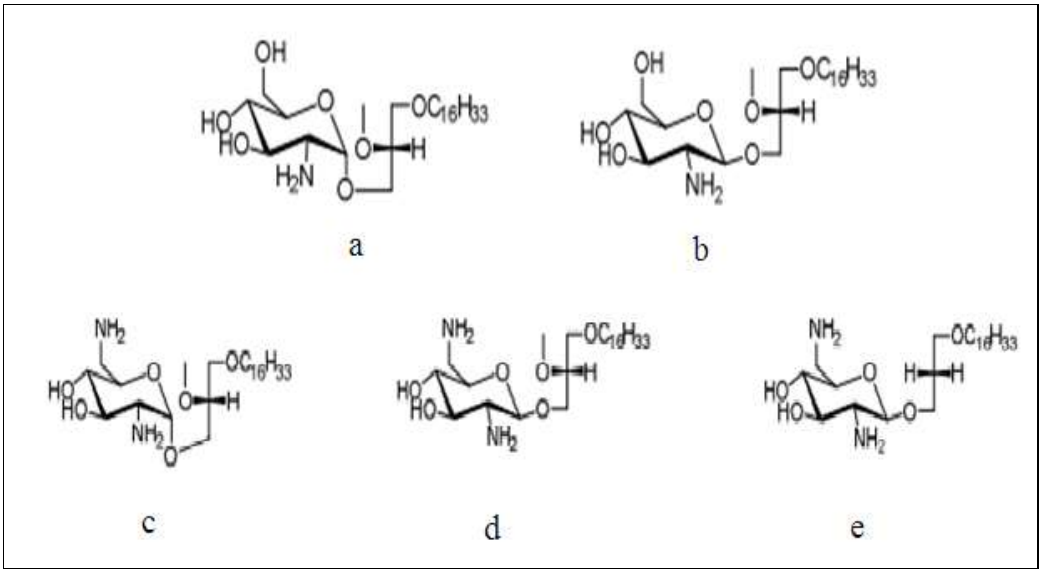

Figure 7: Chemical structures of GAELs with improved cytotoxic activity.

Al-Bujuq *et al* have synthesized and investigated the in vitro cytotoxic effect of 4-O-linked-β-D-galactopyranosyl derivatives of phenolic acid esters including methyl ferulate (Figure 8, a) and methyl vanillate (Figure 8, b) on two human cancer cell lines, which are breast cancer cell line (MCF-7) and prostate cancer cell line (PC-3). The results showed these galactosylated compounds have an improved cytotoxic activity compared with their non-galactosylated compounds [26].

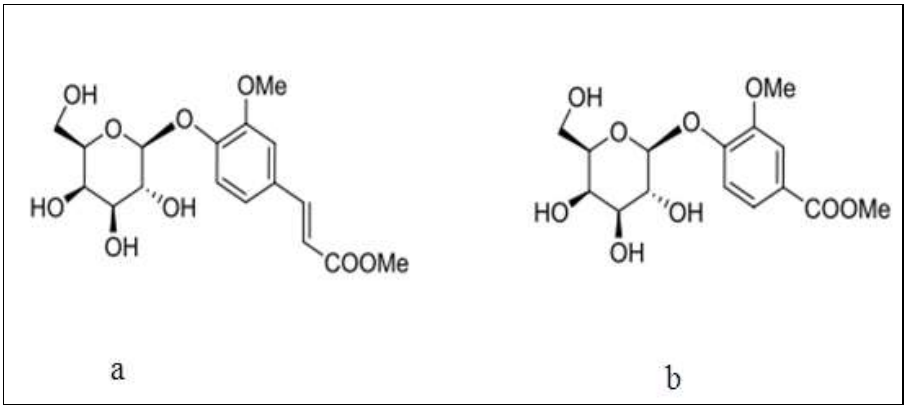

Figure 8: Chemical structures of galactosylated compounds prepared by Al-Bujuq *et al.*

Bashir *et al* have synthesized and studied the in vitro cytotoxic effect of O-β-glucosylated coumarin-pyrazoline derivatives on two human cancer cell lines, which are breast cancer cell line (MCF-7) and esophageal cancer cell line (SKG). The results showed that the O-β-glycosylated compound (Figure 9) has the best antitumor activity versus the test cancer cell lines compared with their non-glycosylated compounds. These results may indicate the importance of glycosylation for improving the site selectivity of the original compounds [27].

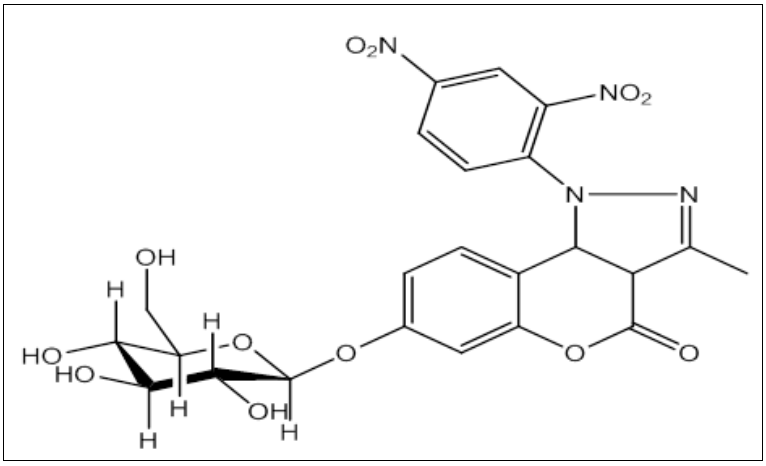

Figure 9: The chemical structure of the O-β-glucosylated compound prepared by Bashir *et al.*

N-glycosylation for enhancing the aglycone cytotoxic activity

Many studies have been carried out to investigate the role of N-linked glycosylation on the cytotoxic activity of their conjugated aglycones [28-30].

Cucciolito *et al* have synthesized a new class of five-coordinate Pt(II) compounds by their conjugating via N-linked sugar using either pyridine or imidazoline linker. These conjugates have been shown to have an improved cytotoxic activity compared with cisplatin on two cancer cell lines including human breast cancer cell line (MCF-7) and epidermoid carcinoma cell lines (A431). The results acquired from X-ray crystallography showed that N-glycosylation has improved the apoptotic activity through better interaction with DNA and proteins. The compounds shown in Figure 10 have reported to possess the best antitumor activity versus the test cancer cell lines [28].

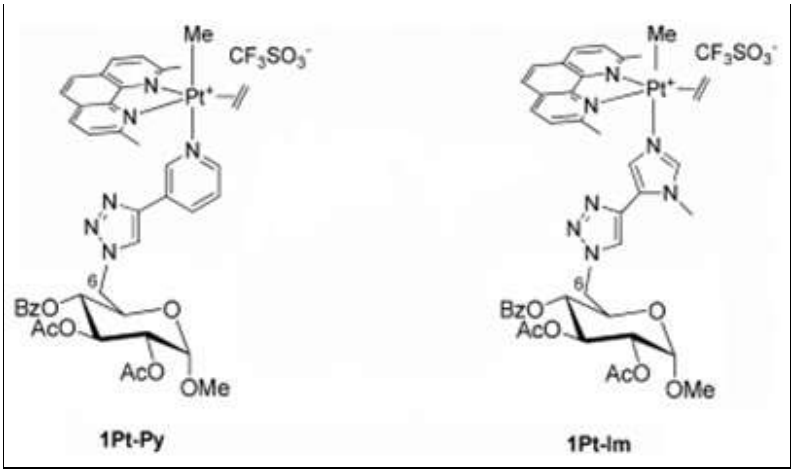

Figure 10: Chemical structures of glycosylated five-coordinate Pt(II) compounds with an improved antitumor activity.

Alminderej *et al* have synthesized a new series of compounds containing 1,2,3-triazolyl-1,3,4-thiadiazole-N-glucoside and examined their cytotoxic activity against two cancer cell lines, which are human breast cancer cell line (MCF-7) and human colorectal carcinoma cell line (HCT-116). The results showed that the compounds shown in Figure 11 have the best activity against the test cancer cell lines. These results indicated the significance of N-glycosylation to afford a new triazole scaffold for improving the cytotoxic activity of these heterocyclic compounds [29].

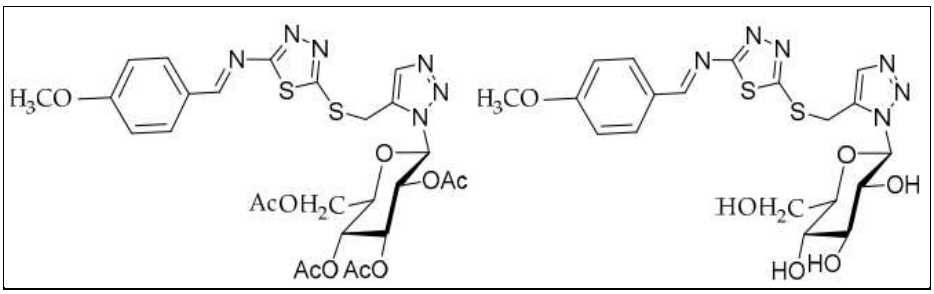

Figure 11: Chemical structures of the conjugates synthesized by Alminderej *et al* with an improved antitumor activity.

Carreira *et al* have synthesized and investigated the cytotoxicity of a novel series of styryl pyrazole N-glucoside against human adenocarcinoma cell line (AGS). The results showed an improvement in the cytotoxicity especially for the compound shown in Figure 12 which has an IC_{50} 73 µM comparing with its non-glycosylated compound having an IC_{50} more than 100µM. This improvement may indicate the importance of N-glycosylation for enhancing the site selectivity based on Warburg phenomena [30].

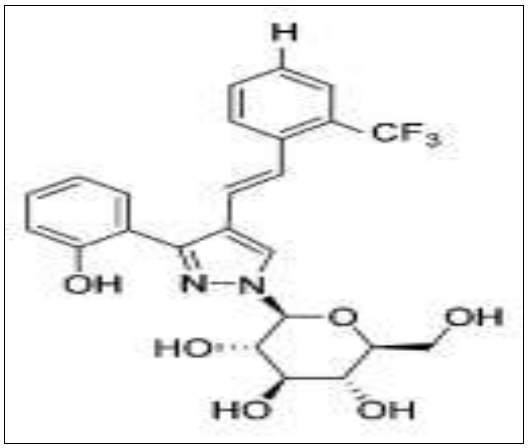

Figure 12: Chemical structure of the N-glycosylated product prepared via Carreira *et al* with an improved antitumor activity.

C- and S-glycosylation for enhancing the aglycone cytotoxic activity

C-glycosylation is a new strategy which investigated to improve the cytotoxic activity and reduce the toxic side effects of the currently available anticancer agents. Cucciolito *et al* have used D-glucose and D-galactose for linking with either C1 or C6 of platinum complex. The compound $1gal_1$-I (Figure 13) was found to possess the best cytotoxic activity compared with the other glycosylated platinum complexes with an IC_{50} 15.2 ± 0.3 µg/ml in murine BALB/c-3T3 cells and 3.9 ± 0.3 µg/ml in fibroblast SVT_2 cells using MTT assay next to 48 hours incubation. This improvement in the cytotoxicity may attribute to the enhancement of complex stability in biological media and to increase the selectivity toward tumor cells depending on Warburg effect [31].

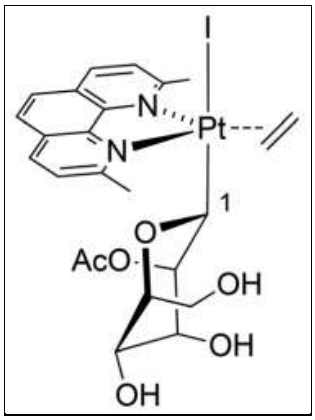

Figure 13: Chemical structure of C-glycosidic compound prepared by Cucciolito *et al* with an improved cytotoxicity.

Abdelhady and Motaal have extracted and identified the compound 8-C-β-D-(3"-O-acetyl) glucopyranosyl apigenin (Figure 14) from the leaves of the plant *Ocimum basilicum*. This compound was found to be highly cytotoxic agent against human colon cancer cell line (HCT-116) compared with 80% crude ethanolic extract of the plant. This improved antitumor activity may indicate the significance of C-glycosylation for enhancing the cytotoxic activity [32].

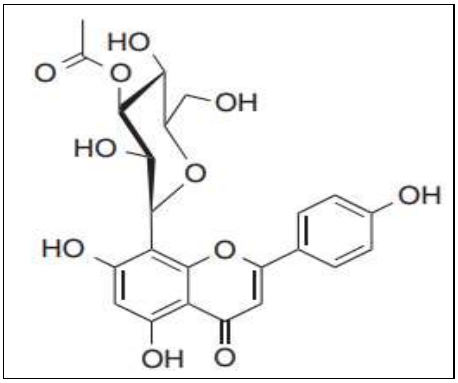

Figure 14: Chemical structure of glycosylated apigenin-based compound isolated by Abdelhady and Motaal.

The influence of S-glycosylation on the cytotoxic activity of various antitumor agents has been highly investigated. For instance, Flefel *et al* have studied the cytotoxic activity of thioglycoside derivatives of (1,3,4-thiadiazolyl)thiaazaspiro[4,5] decane and of thioglycoside derivatives of thiazopyrimidine versus three cancer cell lines, which are HepG-2 (human liver hepatocellular carcinoma), PC-3 (human prostate adenocarcinoma), and HCT-116 (human colorectal carcinoma). The results showed that compounds shown in Figure 15 have an improved cytotoxic activity versus the test cell lines compared with their corresponding aglycones [33].

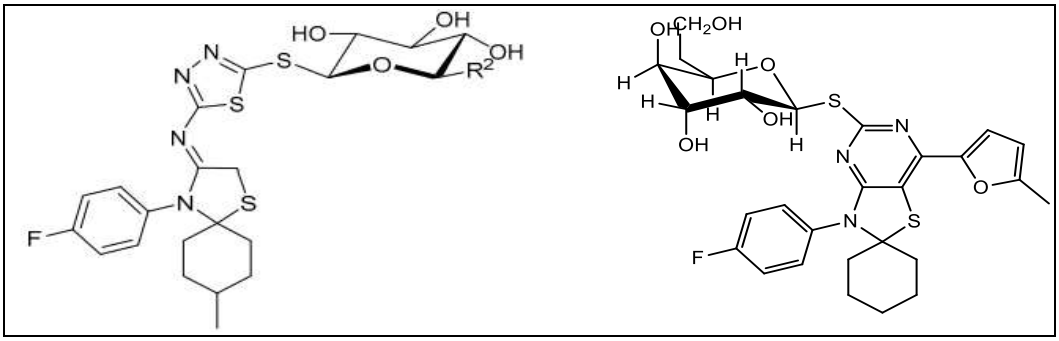

Figure 15: Chemical structures of S-glycosidic products prepared by Flefel *et al* with an enhanced antitumor activity.

Yousif *et al* have synthesized novel thioglycoside derivatives of imidazolyl indole system and investigated their activities against four cancer cell lines including MCF-7, PC3, HCT-116 and HEPG2. The results showed that the compound shown in Figure 16 has a significant antitumor activity against two cancer cell lines, which are MCF-7 with an IC_{50} 80 ± 7 µM and PC3 with an IC_{50} 15 ± 3 µM. This may indicate the enhanced selectivity of its aglycone because of S-glycosylation [34].

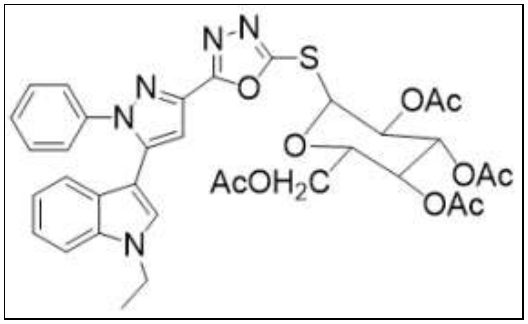

Figure 16: Chemical structure of S-glycosidic product prepared by Yousif *et al* with an enhanced antitumor activity.

Glycosylation for enhancing the antioxidant activity

Oxidative stress defined as the disturbance in the balance between the production of free radicals and the antioxidant defense mechanisms in a biological system. It was found that many pathological conditions such as inflammation, cardiovascular diseases, and cancer are significantly linked to oxidative stress [35]. There are many endogenous antioxidant defense mechanisms to scavenge the free radicals. These mechanisms can be categorized into enzymatic and non-enzymatic based on their modes of action. Superoxide dismutases, glutathione peroxidase, catalase, and glutathione reductase are examples of the enzymatic antioxidant, while glutathione, thioredoxine, and

melatonin are examples of the non-enzymatic endogenous antioxidants [36-40].

To enhance the antioxidant ability of a biological system against free radicals, there are some exogenous antioxidants which are highly effective such as vitamin C, vitamin E, vitamin A, minerals, and polyphenols including flavonoids [41].

Several polysaccharides and glycosyl-conjugates have been recently found to have significant in vitro and in vivo antioxidant potentials. The possible mechanisms of this activity may be attributed to their ability for scavenging the free radicals and chelating the pro-oxidant metals[42].

Many studies concerning the antioxidant activity of glycosyl-conjugates have been performed [43-45]. For instance, Gonzalez-Alfonso *et al* have glycosylated the (-)-epigallocatechin gallate, which is the predominant catechin in green tea (*Camellia Sinensis*), through enzymatic cyclodextrin glucotransferase method at different positions, and subsequently examined their scavenging activity toward ABTS free radicals. The results showed that the compound shown in Figure 17 with an α-glycosylation at position 3' of the ring B has a significant increase in the antioxidant activity compared with its original compound. This improvement in the antioxidant activity may be attributed to the enhanced chemical stability of resulted conjugate [43].

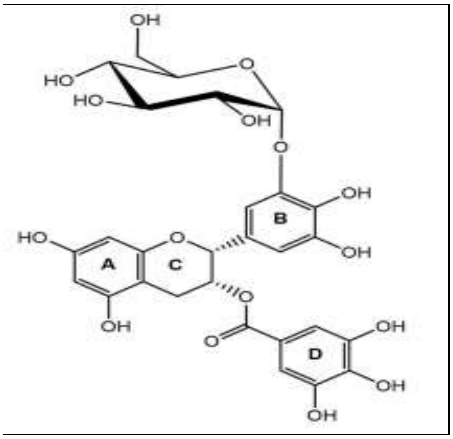

Figure 17: Chemical structure of the semisynthetic product prepared by Gonzalez-Alfonso *et al* with an improved antioxidant activity.

Bellia *et al* have synthesized and examined the antioxidant activity of N- and O-linked β-cyclodextrin of three derivatives of histidine containing dipeptides including carnosine (β-alanine-L-histidine), homocarnosine (γ-aminobutyryl-L-histidine), and anserine (β- alanyl-3-methyl-L-histidine). The results of testing their antioxidant activity towards copper-induced human LDL oxidation showed that both N- and O-β-cyclodextrin-anserine conjugate (Figure 18) have the highest antioxidant effect; and that all glycosylated derivatives had more antioxidant activity than their free histidine-containing dipeptides [44].

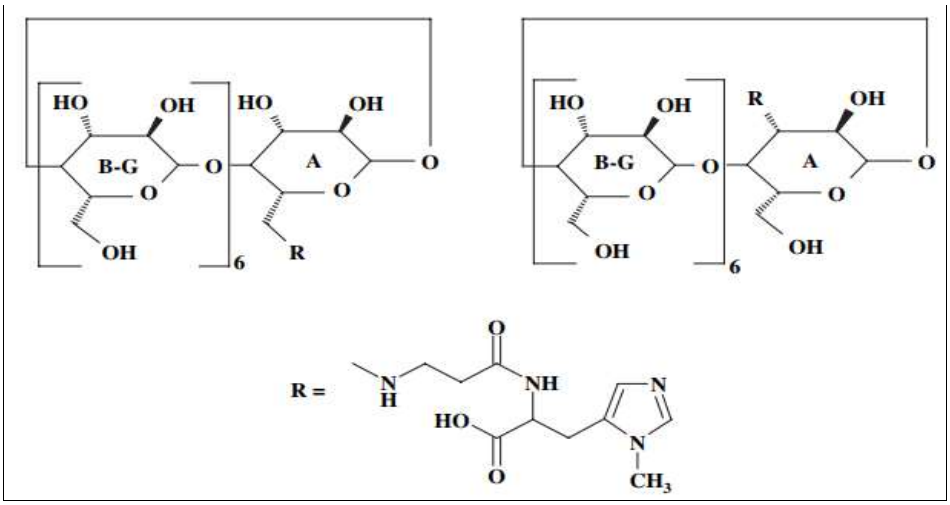

Figure 18: Chemical structures of N- and O- β-cyclodextrin-anserine conjugates with an enhanced antiradical activity.

Zhu *et al* have isolated and identified fourteen types of flavonoids from *Agrimonia pilosa Ledeb* such as taxifolin, luteolin, and rutin. This study examined their potential as antioxidant agents using a DPPH radical scavenging assay and vitamin C as a positive control. The results showed that the chemical modification of these flavonoids through

glycosylation at C6 in the A-ring (Figure 19) has enhanced the antioxidant activity of their original products. This improved antiradical activity may be due to the high uniform distribution of spin density [45].

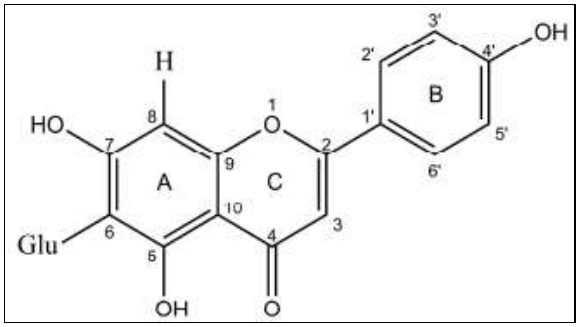

Figure 19: Chemical Structure of the semisynthetic flavonoid prepared by Zhu *et al* with an enhanced antiradical activity.

Glycosylation for enhancing the antibacterial activity

Formerly, it was thought that glycone moieties in glycosidic antibiotics were important to modify their pharmacokinetic features such as aqueous solubility, biodistribution, and bioavailability. Currently, it is believed that these moieties are also important for interacting with the active site of the target. Therefore, the efforts are now focused on the synthesis and modulation of glycone-based antibiotics to create new better tuned antibiotics for better therapeutics [46-49].

Peraman *et al* have synthesized a novel series of different glycosyl-conjugated quinoxaline in an attempt to improve the anti-tubercular activity of the parent product through enhancement of its intercalating potency. The results showed that quinoxaline conjugated with ribose (Figure 20) has the most promising activity against mycobacteria with minimum inhibitory concentration of 0.65 µM. The in silico docking study of this conjugate revealed that DNA gyrase B subunit is the possible site of action [50].

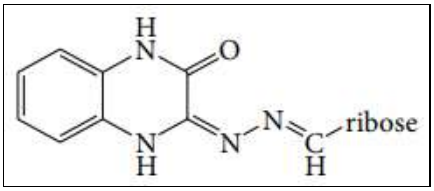

Figure 20: Chemical structure of the glycosylated product synthesized by Peraman *et al as an antituberculosis agent.*

Sganappa *et al* have synthesized and investigated the antibacterial activity of a new series of neomycin-sugar conjugates through a domino synthetic process. The final compounds were tested against *Klebsiella pneumoniae, methicillin resistant Staphylococcus aureus*, and *E. coli.* The results showed that the compounds shown in Figure 21 have the highest activity against *Klebsiella pneumoniae* compared with tetracycline as a positive control [51].

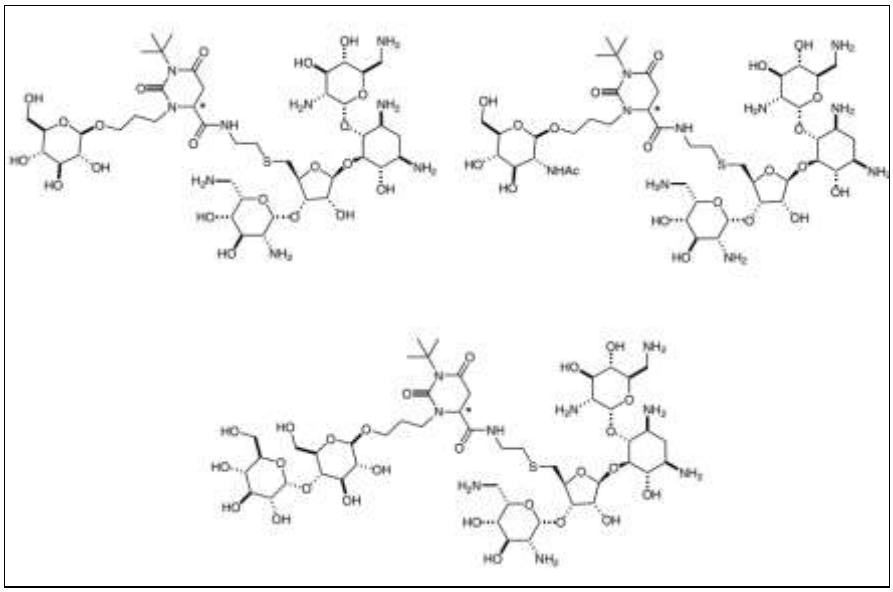

Figure 21: Chemical structures of semisynthetic products prepared by Sganappa *et al* with an improved antibacterial activity versus *Klebsiella spp.*

Choi *et al* have investigated the effects of ciprofloxacin (Figure 22, a) conjugation with mono-6-deoxy-6-aminoethylamino-β-cyclodextrin (β-CD) on its aqueous solubility, bioavailability, and antibacterial activity. In chemical synthesis, β-CD takes the oval shape form (Figure 22, b) in which ciprofloxacin is embedded. The results showed that the ciprofloxacin- β-CD conjugate has seven folds increase in the aqueous solubility than the original drug. Furthermore, this conjugate has a significant increase in the antibacterial activity against *methicillin resistant Staphylococcus aureus* [52].

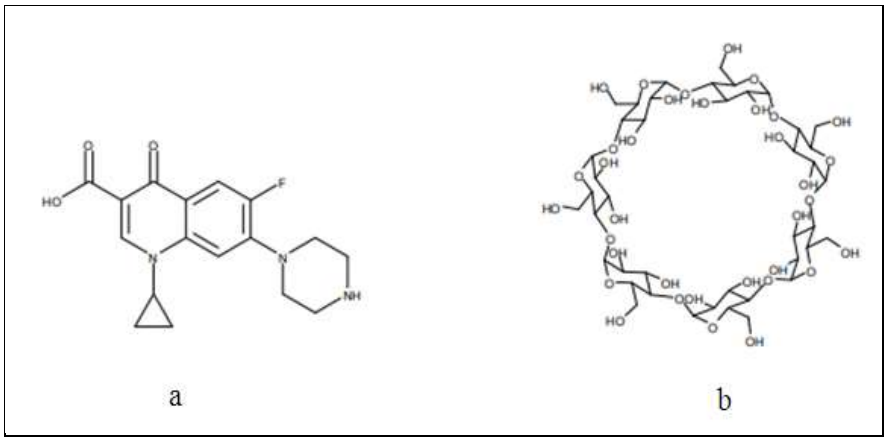

Figure 22: Chemical structure of ciprofloxacin and its glycosylated complex.

CONCLUSION

Glycosylation of active pharmacological agents represented a new research field for enhancing the biological and pharmacokinetic properties of their aglycones. This review article shows some of the new researches in the fields of improving the antitumor, antioxidant, and antibacterial activities of glycosylated products comparing with their pure aglycones with exploring the possible mechanisms of such change in the activities. The listed results may generate a guideline for the development of new products with improved biological activities based on their conjugation with various sugars.

ACKNOWLEDGEMENTS

The authors are very grateful to the University of Mosul/College of Pharmacy for their provided facilities, which helped to improve the quality of this work.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Spiro RG, 2002. Protein glycosylation: Nature, distribution, enzymatic formation, and disease implication of glycopeptide bonds. *Glycobiology* 12(4):43R-56R.
2. Clark GF, Oehninger S, Seppälä M, 1996. Role of glycoconjugates in cellular communication in the human reproductive system. *Molecular Human Reproduction* 2(7):513-517.
3. Berg JM, Tymoczko JL, Stryer L, 2002. *Biochemistry.* W.H. Freeman and Company: New York. 5th edition: pp. 306-309.
4. Zhang X, Wang Y, 2016. Glycosylation quality control by the golgi structure. *Journal of Molecular Biology* 428(16):3183-3193.
5. Potter M, Newport E, Morten KJ, 2016. The Warburg effect: 80 years on. *Biochemical Society Transaction* 44:1499-1505.
6. Hanahan D, Weinberg RA, 2011. Hallmarks of cancer: The next generation. *Cell* 144(5):646-674.
7. Zu XL, Guppy M, 2004. Cancer metabolism: facts, fantasy, and fiction. *Biochemical and Biophysical Research Communications* 313:459-465.
8. Liberti MV, Locasale JW, 2016. The Warburg effect: how does it benefit cancer cells? *Trends in Biochemical Sciences* 41(3):211-218.
9. Altenberg B, Greulich KO, 2004. Genes of glycolysis are ubiquitously overexpressed in 24 cancer classes. *Genomics* 84(6):1014-1020.
10. Ben-Haim S, Ell P, 2009. ^{18}F-FDG PET and PET/CT in the evaluation of cancer treatment response. *Journal of Nuclear Medicine* 50(1):88-100.
11. Herrmann AK, Benz MR, Krause BJ, Pomykala KL, Buck AK, Czernin J, 2011. ^{18}F-FDG-PET/CT in evaluating response to therapy in solid tumors: Where we are and where we can go. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging* 55(6):620-632.
12. Cal PM, Matos MJ, Bernardes GJL, 2017. Trends in therapeutic drug conjugate for bacterial diseases: a patent review. *Expert Opinion on Therapeutic Patents* 27(2):179-189.
13. Makino T, Shimizu R, Kanemaru M, Suzuki Y, Moriwaki M, Mizukami H, 2009. Enzymatically

modified isoquercitrin, α-oligoglucosyl quercetin 3-O-glucoside, is absorbed more easily than other quercetin glycosides or aglycone after oral administration in rats. *Biological and Pharmaceutical Bulletin* 32:2034-2040.

14. Pottenuzzo A, Pigot R, Ronconi L, 2015. Metal-based glycoconjugates and their potential in targeting anticancer chemotherapy. *Metallodrugs* 1:36-61.
15. Pohl J, Bertram B, Hilgard P, Nowrousian MR, Stüben J, Wiessler, B, 1995. D-19575-a sugar-linked isophosphoramide mustard derivative exploiting transmembrane glucose transport. *Cancer Chemotherapy and Pharmacology* 35(5):364-370.
16. Briasoulis E, Judson I, Pavlidis N, Beale P, Wanders J, Groot Y, *et al*., 2000. Phase I trial of 6-hour infusion of glufosfamide, a new alkylating agent with potentially enhanced selectivity for tumors that overexpress transmembrane glucose transporters: A study of the European Organization for Research and Treatment of Cancer Early Clinical Studies Group. *Journal of Clinical Oncology* 18(20): 3535-3544.
17. Mustafa YF, Oglah MK, Bashir MK, 2020. Conjugation of sinapic acid analogues with 5-Fluorouracil: Synthesis, preliminary cytotoxicity, and release study. *Systematic Reviews in Pharmacy* 11(3):482-489.
18. Mustafa YF, 2019. Synthesis, characterization and preliminary cytotoxic study of sinapic acid and its analogues. *Journal of Global Pharma Technology* 11(9):1-10.
19. Mustafa YF, Najem MA, Tawffiq ZS, 2018. Coumarins from Creston apple seeds: Isolation, chemical modification, and cytotoxicity study. *Journal of Applied Pharmaceutical Science* 8(8):49-56.
20. Khalil RR, Mustafa YF, 2020. Phytochemical, antioxidant and antitumor studies of coumarins extracted from Granny Smith apple seeds by different methods. *Systematic Reviews in Pharmacy* 11(2):57-63.
21. Mandai T, Okumoto H, Oshitari T, Nakanishi K, Mikuni K, Hara K, *et al*., 2001. Synthesis and biological evaluation of water soluble taxoids bearing sugar moieties. *Heterocycles* 54(2):561-566.
22. Lin YS, Tungpradit R, Sinchaikul S, An FM, Liu DZ, Phutrakul S, *et al*., 2008. Targeting the delivery of glycan-based paclitaxel prodrugs to cancer cells via glucose transporters. *Journal of Medicinal Chemistry* 51(23):7428-7441.
23. Zi CT, Yang L, Kong QH, Li HM, Yang XZ, Ding ZT, *et al*., 2019. Glucoside derivatives of podophyllotoxin: synthesis, physiochemical, and cytotoxicity. *Drug Design, Development and Therapy* 13:3683-3692.
24. Ma J, Wang Q, Huang Z, Yang X, Nie Q, Hao W, *et al*., 2017. Glycosylated platinum (IV) complexes as substrates for glucose transporters (GLUTs) and organic cation transporters (OCTs) exhibited cancer targeting and human serum albumin binding properties for drug delivery. *The Journal of Medicinal Chemistry* 60:5736-5748.
25. Ogunsina M, Samadder P, Idowu T, Arthur G, Schweizer F, 2013. Design, synthesis and evaluation of cytotoxic properties of bisaminoglucosylated antitumor ether lipids against cancer cells and cancer stem cells. *Med Chem Comm*. DOI: 10.1039/C6MD00328A.
26. Al-Bujuq N, Arar S, Khalil R, 2018. Synthesis and cytotoxic activity of 4-O-β-D-galactopyranosyl derivatives of phenolic acids esters. *Natural Product Research* 32(22):2663-2669.
27. Bashir MK, Al-Omari NA, Omar AO, 2018. Glucose conjugation of coumarin-pyrazoline derivatives as a promising strategy for cancer cell targeting. *International Journal of Enhanced Research in Science, Technology & Engineering* 7(6):19-26.
28. Cucciolito ME, D'Amora A, DeFeo G, Ferraro G, Giorgio A, Petruk G, *et al*., 2017. Five-coordinate platinum (II) compounds containing sugar ligands: synthesis, characterization, cytotoxic activity, and interaction with biological macromolecules. *Inorganic Chemistry*; DOI: 10.1021/acs.inorgchem.7b03118.
29. Alminderej FM, Elganzory HH, El-Bayaa MN, Awad HM, El-Sayed WA, 2019. Synthesis and cytotoxic activity of new 1,3,4-thiadiazole thioglycosides and 1,2,3-triazolyl-1,3,4-thiadiazole N-glucosides. *Molecules* 24:3738-3752.
30. Carreira ARF, Pereira DM, Andrade PB, Valentão P, Silva AMS, Braga SS, *et al*., 2019. Novel styrylpyrazole-glucosides and their dioxolo-bridged doppelganger: synthesis and cytotoxicity. *New Journal of Chemistry* 43:8299-8310.
31. Cucciolito ME, Bossa FDL, Esposito R, Ferraro G, Iadonisi A, Petruk G, *et al*., 2018. C-glycosylation in platinum based agents: a viable strategy to improve cytotoxicity and selectivity. *Inorganic Chemistry Frontiers* 5:2921-2933.
32. Abdelhady MIS, Motaal AA, 2016. A cytotoxic C-glycosylated derivative of apegenin from the leaves of *Ocimum basilicum var. thyrsiflorum*. *Brazilian Journal of Pharmacognosy* 26:763-766.
33. Flefel EM, El-Sayed WA, Mohamed AM, El-Sofany WI, and Awad HM, 2017. Synthesis and anticancer activity of new 1-thia-4-azaspiro[4.5] decane, their derived thiazolopyrimidine and 1,2,3-thiadiazole thioglycosides. *Molecules* 22(170). DOI: 10.3390/molecules22010170.
34. Yousif MNM, Hussein HAR, Yousif NM, El-Manawaty MA, El-Sayed WA, 2019. Synthesis and anticancer activity of novel 2-phenylindole linked imidazolothiazole, thiazolo-s-triazine and imidazolyl-sugar system. *Journal of Applied Pharmaceutical Science* 9 (1):6-14.
35. Betteridge DJ, 2000. What is oxidative stress? *Metabolism* 49(2):3-8.
36. Oglah MK, Mustafa YF, Bashir MK, Jasim MH, 2020. Curcumin and its derivatives: A review of their biological activities. *Systematic Reviews in Pharmacy* 11(3):472-481.

37. Mahmood AAJ, Mustafa YF, Abdulstaar M, 2014. New coumarinic azo-derivatives of metoclopramide and diphenhydramine: Synthesis and in vitro testing for cholinesterase inhibitory effect and protection ability against chlorpyrifos. *International Medical Journal Malaysia* 13(1):3-12.
38. Aldewachi H, Mustafa YF, Najm R, Ammar F, 2020. Adulteration of slimming products and its detection methods. *Systematic Reviews in Pharmacy* 11(3):289-296.
39. Stirrat, C.G., Cameron, A.D., Mills, N.L., Dunn, F.G. A clinical scoring system in undifferentiated chest pain predicting undetectable troponin concentration (2013) Journal of Cardiovascular Disease Research, 4 (2), pp. 98-101. DOI: 10.1016/j.jcdr.2013.05.003
40. Nejres AM, Mustafa YF, Aldewachi HS, 2020. Evaluation of natural asphalt properties treated with egg shell waste and low density polyethylene. International Journal of Pavement Engineering. https://doi.org/10.1080/10298436.2020.1728534
41. Oglah MK, Mustafa YF, 2020. Curcumin analogs: synthesis and biological activities. *Medicinal Chemistry Research* 29(3):479-86.
42. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE, 2014. Oxidative stress: An essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiological Reviews* 94:329-354.
43. Wang J, Hu S, Nie S, Yu Q, Xie M, 2016. Reviews on mechanisms of in vitro antioxidant activity of polysaccharides. *Oxidative Stress and Cellular Longevity*. DOI: org/10.1155/2016/5692852.
44. Gonzalez-Alfonso JL, Peňalver P, Ballesteros AO, Morales JC, Plou FJ, 2019. Effect of α-glucosylation on the stability, antioxidant properties, toxicity, and neuroprotective activity of (-)-epigallocatechin gallate. *Froutiers in Nutrition* 6. https://doi.org/ 10.3389/fnut.2019.00030.
45. Bellia F, Amorini AM, Mendola DL, Vecchino G, Tavazzi B, Giardina B, *et al*., 2008. New glycosidic derivatives of histidine-containing dipeptides with antioxidant properties and resistant to carnosinase activity. *European Journal of Medicinal Chemistry* 43:373-380.
46. Zhu L, Chen J, Tan J, Liu X, Wang B, 2017. Flavonoids from *Agrimonia pilosa Ledeb*: free radical scavenging and DNA oxidative damage protection activities and analysis of bioactivity-structure relationship based on molecular and electronic structures. *Molecules* 22 (195). https://doi.org/10.3390/molecules22030195.
47. Kren V, Rezanka TT, 2008. Sweet antibiotics - the role of glycosidic residues in antibiotic and antitumor activity and their randomization. *FEMS Microbiological Review* 32:858-889.
48. Mustafa YF, Khalil RR, Mohammed ET, 2020. Antimicrobial activity of aqueous extracts acquired from the seeds of two apples' cultivars. *Systematic Reviews in Pharmacy* 11(2):382-287.
49. Mohammed ET, Mustafa YF, 2020. Coumarins from Red Delicious apple seeds : Extraction , phytochemical analysis , and evaluation as antimicrobial agents. *Systematic Reviews in Pharmacy* 11(2):64-70.
50. Mustafa YF, 2018. Synthesis, characterization and antibacterial activity of novel heterocycle, coumacine, and two of its derivatives. *Saudi Pharmaceutical Journal* 26(6):870-875.
51. Peraman R, Kuppusamy R, Killi SK, Reddy YP, 2016. New conjugates of quinoxaline as potent antitubercular and antibacterial agents. *International Journal of Medicinal Chemistry*. https://doi.org/10.1155/2016/6471352.
52. Sganappa A, Bellucci MC, Nizet V, Tor Y, Volonterio A., 2016. Multicomponent domino synthesis and antibacterial activity of neomycin-sugar conjugates. *Synthesis* 48: A-H. https://doi.org/10.1055/s-0035-1562727
53. Choi JM, Park K, Lee B, Jeong D, Dindulkar SD, Choi Y, *et al*., 2017. Solubility and bioavailability enhancement of ciprofloxacin by induced oval-shaped mono-6-deoxy-6-amino-β-cyclodextrin. *Carbohydrate Polymers* 1:118-128.