A Review on Biological Activities of Sugars and Sugar Derivatives

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ABSTRACT: Sugar and sugar derivatives have numerous reported biological activities. Sugar moieties in many therapeutically important compounds have influence on their pharmacological activities. Structure activity relationship studies have revealed the importance of sugar moieties in the structure of many clinically used drugs. This review focuses on the major biological activities such as anti-cancer, anti-diabetic, analgesic, anti-inflammatory, antiviral and antimicrobial activities of sugars and their derivatives including modified or synthetic sugar derivatives. The available reported structure activity relationship studies have also been described in this review. Biological investigation of different activities of sugar derivatives proves their suitability as one of the interesting classes of molecules for development of new drugs.

Key words: Sugar, sugar derivative, anti-cancer, anti-microbial, analgesic, anti-inflammatory, anti-diabetic

INTRODUCTION

Sugars and sugar derivatives have important roles in the field of medicine because of their multifaceted pharmacological activities. The roles of sugar moiety in the biological activity of different therapeutically important compounds are becoming more and more evident from their structure activity relationship (SAR) studies. The commonly known monosaccharides and disaccharides are shown in Figure 1: ribose (1), glucose (2), mannose (3), galactose (4), allose (5), xylose (6), fructose (7), N-acetylglucosamine (8), N-acetylenuraminic acid (9), sucrose (10), lactose (11), mannitol (12) and fructose 1, 6 bisphosphate (13). Naturally occurring sugars and sugar derivatives have been used clinically for a long time. For example, mannitol (12) a naturally occurring sugar alcohol is synthesized industrially for application in the treatment of cerebral edema and increased intracranial pressure. Fructose-1,6 bisphosphate (13) is reported to possess anti-inflammatory activity.

Figure 2 shows various therapeutically important sugar derivatives. Streptomycin (14), gentamicin (15) and other aminoglycosides and macrolide antibiotics, for example, erythromycin (16), azithromycin (17) and others contain sugar moieties in their structure. Sugars are extensively used in the synthesis of nucleoside and nucleotide analogues. Zidovudine (18) and ribavirin (19) are nucleoside antiviral agents which contains ribose as the sugar part. Neuraminidase inhibitors like zanamivir (20) oseltamivir (21) are monosaccharide mimics. Antibiotic anticancer agents viz daunorubicin (22), doxorubicin (23) and bleomycin (24) also have sugar moieties in their structures. Miglustat (25) and miglitol (26) are iminosugars which are used for the treatment of Gaucher disease and diabetes mellitus, respectively. Voglibose (27), an antidiabetic agent is a sugar derivative. Clinically used sodium dependent glucose cotransporter type 2 (SGLT2) inhibitors such as empagliflozin (28), dapagliflozin (29) have a D-glucose moiety attached to their structures. Sugars are integral part of compounds known as glycosides. Glycosides such as digoxin (30) and ouabain (31) have long been used in the treatment of diseases like congestive heart failure and...
arrhythmia, respectively. Thus, it can be said that sugar and sugar derivatives are among the interesting compounds that can be explored in search of new drugs.


Inspired by the multifarious biological activities and therapeutic applications of sugars and their derivatives, we recently reported the synthesis of several sugar derivatives and evaluated them for biological activities.\textsuperscript{17,18} To realize the biological importance of sugars and their derivatives we decided to undertake a thorough literature search for understanding the present level of research activities as well as the spectrum of biological activities reported so far. The current article focused mainly on the synthetic sugar derivatives, modifications of existing sugar containing drugs and their biological activity. Sugar containing nucleoside and nucleotide derivatives have not been included in this review. The major biological activities have been summarized for gaining comprehensive knowledge.

MATERIALS AND METHODS

Literature survey was carried out thoroughly to collect all available data on the databases like PubMed, Science Direct, Scopus and Google Scholar. The time range selected was in between the year 2000 to 2021. The keywords used were “sugar”, “sugar derivative”, “modified sugar”, “monosaccharide”, “disaccharide”. Afterwards, for each section, particular key words “anticancer”, “anti-diabetic”, “analgesic”, “anti-inflammatory”, “antiviral”, “antibacterial”, “antifungal” associated with sugar and sugar derivatives were searched. Articles were restricted to English language. All data from any unreliable sources were excluded.

RESULTS

Anticancer activity. Many anticancer drugs contain sugar moieties in their structures which are responsible for their pharmacological action and selectivity. The sugar moiety in anthracyclines such as doxorubicin serves as inhibitor for DNA topoisomerase II as non-intercalating external moiety.\textsuperscript{11} As drug resistance has become a concern in treatment of cancer with anthracyclines, new analogues of these agents with modified sugar moiety are being investigated. Figure 3 summarizes the compounds having sugar moieties in their structures with potential anticancer activities. Sabarubicin (32), a disaccharide analogue of doxorubicin, is now under clinical trials. This compound exhibited more pronounced anti-tumor activity than the parent compound in preclinical in vivo models.\textsuperscript{19} Several novel disaccharide analogues of daunorubicin have been reported to show optimistic result in doxorubicin resistant K562/Dox cells with IC\textsubscript{50} value in 200-1100nM range.\textsuperscript{20} The disaccharide analogue, compound 33, was found to be 17 times more potent than daunorubicin. This compound also had equal IC\textsubscript{50} value in both drug sensitive and drug resistant cells. Structure activity relationship (SAR) study revealed that orientation of the 3-OH group of the second sugar moiety and its substitution could have major influence on the anticancer activity of the molecule. Disaccharide moiety of the antitumor antibiotic bleomycin is responsible for the selective action of the agent on tumor cells. Bleomycin preferentially targeted human breast carcinoma cell line (MCF-7) compared to normal breast cell line (MCF-10A) whereas its analogue without the disaccharide moiety did not target either of the cell lines.\textsuperscript{21} There are a number of synthetic compounds with sugar moieties present in their structures displayed anticancer activity in both in vitro and in vivo experiments. Flefel et al. (2013) synthesized several sugar hydrazone of pyrazole derivatives that were tested against human cervix carcinoma cell line (HeLa) and breast cancer cell line (MCF-7).\textsuperscript{22} In these tests, pyrazole derivatives with acyclic D-glucopentitolyl moiety (34) had an equal IC\textsubscript{50} value of 3.60\mu M compared to that of cisplatin against HeLa cell line and a lower IC\textsubscript{50} value of 2.52\mu M against MCF-7 cell line compared to 2.80\mu M of cisplatin. Synthesized furyl-thiadiazolyl-oxidiazole acyclic sugar derivatives containing D-mannose and D-ribose moieties have been subjected to lactose dehydrogenase (LDH) assay in liver cancer cell lines (HEPG2 and RPE-1).\textsuperscript{23} Among these the D-mannose containing derivative (35) had the most potential activity in HEPG2 cell line with an IC\textsubscript{50} value of 4.2\mu M. A series of glycosylated indolocarbazole
analogue with more than twenty different sugar moieties targeting DNA-topoisomerase I has been synthesized and the β-D-ribofuranose analogue (36) has been found to be the most potent. Disaccharide analogue of genistein (37) showed more cytotoxic activity than genistein itself. This analogue particularly causes mitotic delay and alteration of microtubule array. Appearance of multipolar microtubule has also been associated with the molecule. From all these examples, it is evident that sugar moieties play critical role in the pharmacological action of compounds with anticancer and antitumor property.

Figure 3. Structures of some synthesized sugar derivatives with reported anticancer activity (32-37).

Figure 4. Structures of some synthesized sugar derivatives with anti-diabetic effect (38-46).
Anti-diabetic activity. Type 2 diabetes is characterized by insulin resistance and subsequent hyperglycemia. Varieties of oral medications are available for management of this metabolic disorder. Many sugar and modified sugar derivatives have been reported with potential antidiabetic effects. In streptozotocin-nicotinamide induced diabetic rats, 31.3% decrease in fasting blood glucose was observed upon replacing 10% of sucrose by D-xylose. In this study it was found that D-xylose regenerated pancreas tissue and suppressed phosphoenolpyruvate carboxylase which is a major rate limiting enzyme in gluconeogenesis process.

SGLT2 inhibitors lower the reabsorption of glucose through renal proximal tubule. In an effort to discover new SGLT2 inhibitors Goodwin et al. (2009) reported several L-xylose derived SGLT2 inhibitors. Among these compounds, compound 38 (Figure 4) showed the highest glycosuric activity with IC$_{50}$ value of 14nM for SGLT2 compared to standard dapagliflozin (IC$_{50}$ = 4.8nM). Several lipophilic D-xylose derivatives have been reported as antidiabetic agent, of which compound 39 is the most potent derivative. This derivative activated the AMP-activated protein kinase α, which in turn induced glucose transporter-4 (GLUT-4) in the plasma membranes of myotubes and augmented the uptake of glucose. 3-O-methyl-D-glucose (40), which is a non-metabolizable analogue of glucose, also increased the uptake of glucose in myotubes. However, the mechanism is not similar to that of D-xylose derivatives. 3-O-methyl-D-glucose did not have effect on the abundance of GLUT-4 located on the plasma membrane of myotubes rather the evidences support the idea that it increases the intrinsic activity of GLUT-4.

Abnormally elevated hepatic glucose output has been observed in type 2 diabetes patients due to increased glycogenolysis. Inhibition of the enzyme glycogen phosphorylase (GP) can reduce the level of glycogenolysis. Series of glucose derived GP inhibitors have been developed and these inhibitors are more active than xylose derived inhibitors. SAR studies revealed that modification at glucose group is usually associated with decreased or diminished enzyme inhibitory activity. Several glucose based spiro-oxathiazole derivatives have been synthesized targeting the catalytic site of GP and among these derivatives, compound 41 was identified to be the most active derivative. The compound 35 had a low K$_s$ value of 160nM for rabbit muscle GP (RMGP) in vitro and decreased blood glucose level by approximately 43% at a dose of 60mg/kg. 1-(β-D-glucopyranosyl)-4-[ (acridin-9-on-2-yl)amino]pyrimidin-2-one (42) and 2-( β -D- glucopyranosyl)-4(5)-(2-naphthyl)-imidazole (43) are the two most potent reported glucose based GP inhibitors with K$_s$ values of 71nM and 31nM respectively. Compound 43 also showed low IC$_{50}$ value of 3.5µM as SGLT2 inhibitor, making it the very first dual inhibitor of SGLT2 and GP.

Another class of anti-diabetic medication, α-glucosidase inhibitors, limits the absorption of glucose by competitively inhibiting intestinal α-glucosidases responsible for conversion of carbohydrates into simple absorbable form. Acarbose, miglitol and voglibose are the major drugs in this class that are used for controlling type 2 diabetes. Acarbose is a polysaccharide whereas miglitol (26) and voglibose (27) are monosaccharide derivatives. Miglitol is an iminosugar, more specifically deoxyxojirimycin derivative whereas voglibose is a valiolamine derivative. Therefore, more and more iminosugar and aminosugars are being investigated for α-glucosidase activity. Several classes of iminosugar derivatives such as dihydroxymethyl piperidine and pyrrolidine, arabinoinofuranoses, polyhydroxy pyrrolidine, N-alkylated, triazole iminosugars are notable. Among these compounds investigated, compound 44 exhibited very low IC$_{50}$ value of 0.028µM for rice α-glucosidase. Compound 45, an arabinofuranose iminosugar has been found to be as effective as miglitol for lowering post prandial glucose level with relatively 10 times lower dose. Among the aminosugar derivatives, N-substituted-1-
aminomethyl-β-D-glucopyranoside and several other pseudo aminosugars were investigated.\textsuperscript{38} Compound 46, a cinnamic amide derivative showed significant yeast α-glucosidase inhibitory activity with IC\textsubscript{50} value of 2.3μM.\textsuperscript{41}

**Analgesic and anti-inflammatory activity.** A number of sugar derivatives have shown promising analgesic and anti-inflammatory activity.\textsuperscript{17,18} Structures of some sugar derived analgesic and anti-inflammatory agents are depicted in Figure 5. D-ribose when used at a dose of 5g, 3 times a day for 3 weeks in patients with fibromyalgia, has shown improvement in the clinical outcomes of the disease including 15.6% reduction of pain.\textsuperscript{42,43} Treatment of nephrotoxicity caused by cisplatin with D-ribose at a dose of 400mg/kg body weight in mice model has shown that, the monosaccharide reduced the elevated levels of renal inflammatory biomarkers like tumor necrosis factor (TNF-α), renal monocyte chemoattractant protein (MCP)-1 and renal expression of intercellular adhesion molecule (ICAM)-1 mRNA.\textsuperscript{44} In a similar study, it has been reported that D-allose also attenuates cisplatin induced nephrotoxicity via reducing the renal inflammatory biomarkers like D-ribose as described.\textsuperscript{45} In two different studies, D-ribose and D-allose exerted anti-inflammatory effect in ischemia and reperfusion induced renal injury in mice at a dose of 400mg/kg significantly decreasing the level of cytokine-induced neutrophil chemoattractant-1 and myeloperoxidase.\textsuperscript{46,47} Additionally, D-allose has exerted anti-inflammatory effect in cerebral ischemia-reperfusion injury and reduced the overexpressed levels of inflammatory cytokines.\textsuperscript{48,49} D-ribose-L-cysteine has been shown to attenuate cortisone mediated oxido-inflammatory effect in mice exposed to mild chronic stress.\textsuperscript{50}

Rahman et al. (2020) synthesized several derivatives of α-D ribofuranose derivatives with potent analgesic and anti-inflammatory activity.\textsuperscript{17} Compound 47 showed the highest analgesic activity in both tail flick and acetic acid writhing method among the synthesized derivatives. Compound 47 and 48 exhibited significant anti-inflammatory activity in carrageenan induced paw edema assay with percentage paw edema inhibition of 82.6% and 87.6%, respectively, when compared to 95.6% inhibition by aceclofenac at a dose of 100mg/kg after 4\textsuperscript{th} hour of injection of carrageenan. In a similar study of α-D ribofuranose derivatives, five analogues were synthesized where all the compounds showed anti-inflammatory activity with percent paw edema inhibition in the range of 78.32-95.13% at 4\textsuperscript{th} hour after carrageenan administration.\textsuperscript{18} In this study, compound 49 exhibited 59.74% and 79.74% inhibition of writhing at the doses of 25 and 50mg/kg, respectively, where the standard diclofenac showed writhing inhibition of 83.19%. This compound also had the highest reaction time in tail flick method.

![Figure 5. Structures of some synthesized sugar derivatives with analgesic and anti-inflammatory properties (47-52).](image-url)
2-Amino-2-deoxy-D-glucose (50) also known as glucosamine, is used in osteoarthritis and different musculoskeletal diseases. Glucosamine is reported to reduce interleukin-1β (IL-1β) and TNF-α induced activation of synovial cells and endothelial cells, respectively. It was also observed that glucosamine sulfate repressed the activity of TNF-α, IL-1β, and prostaglandin E₂ (PGE₂) in macrophage. Recent study suggests, that co-administration of celecoxib with glucosamine has synergistic action supporting their combined use in osteoarthritis.

Several benzimidazole sugar conjugate with anti-inflammatory effect have been synthesized of which compound 51 and 52 had considerable activity. The mannosylated derivative 52 exhibited 72% reduction of edema in carrageenan induced paw edema assay which is comparable to 73% reduction of edema by diclofenac. The compound also had greater anti-inflammatory activity than corresponding non sugar benzimidazole derivative which supports the idea that sugar moiety have role in the biological activity exerted by the molecule. Structure activity relationship study also suggested that the biological activity depends on the position of linkage of sugar moiety with benzimidazole ring i.e. conjugates linked at position 3 had more pronounced action than conjugates linked at position 5.

**Antiviral activity.** A plethora of nucleosides containing different sugar moieties possess antiviral activity. However, there are examples of modified sugar analogues alone having antiviral activity. Zanamivir (17) and oseltamivir (18) used in anti-influenza therapy are monosaccharide mimics that were originally designed based on the structure of sialic acid or N-acetylneuraminic acid (9). He et al. (2020) synthesized a number of diazide sialic acid derivatives of which compound 53 (Figure 6) had IC₅₀ value of 1.41µM against zika virus and compound 54 exhibited potent anti-human rhinovirus activity with IC₅₀ value of 0.93µM. Rota et al. (2017) reported some perfluorinated derivatives of sialic acid which were investigated for in vitro and in
Newcastle disease virus neuraminidase inhibitory activity. Among the derivatives, compound 55 had the lowest IC$_{50}$ value of 2.4µM which is supported by the fact that CF$_3$ group of the compound had an additional interaction with Tyr 299 residue of neuraminidase in in silico study. Triterpene derivatives of sialic acids have also been investigated for antiviral activity. Compound 56 had an IC$_{50}$ value of 41.2 µM in in vitro anti-influenza assay which is comparable to 46.5µM of oseltamivir. In another study, compound 57 showed potent sialidase inhibitory activity of 89.9%, 64.9% and 70.7% against H1N1, H3N2 and H5N3 strains of influenza virus, respectively.

Figure 7. Structures of some synthesized sugar derivatives with antibacterial and antifungal activity (62-82).
The iminosugars are another important class of sugar derivative in the context of antiviral activity.\textsuperscript{64} 1-Deoxynojirimycin (58) is one of the earliest iminosugar derivatives with antiviral activity along with anti-diabetic effect by dint of its α-glucosidase inhibitory activity. This iminosugar and its derivatives have been investigated against hepatitis B virus, hepatitis C virus, human immunodeficiency virus and dengue virus.\textsuperscript{65-67} Recently, N-(9-methoxynonyl)-1-deoxynojirimycin (59) also known as UV-4 and another iminosugar derivative celgosivir (60) have been reported to inhibit replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell culture.\textsuperscript{68} Celgosivir, the prodrug form of castanospermine (61) reduced SARS-CoV-2 replication in dose dependent manner. However, the mechanism of action underlying replication inhibition of SARS-CoV-2 by UV-4 and celgosivir is still unknown. Previously, these two compounds were reported to be effective against dengue virus by inhibition of endoplasmic reticulum α-glucosidase.\textsuperscript{69-70} Similar mechanism was observed for celgosivir against replication of Zika virus.\textsuperscript{71} The active form of celgosivir, castanospermine has also been reported to reduce Zika viral load in murine model.\textsuperscript{72} Figure 6 represents the structures of sugar derivative compounds with antiviral activity.

**Antibacterial and antifungal activity.** Aminoglycoside and macrolide antibiotics contain sugar moiety in their structure.\textsuperscript{73} Despite their usefulness, these antibiotics are becoming ineffective due to development of resistance cases. Figure 7 depicts synthesised sugar derivatives with antibacterial and antifungal properties. Modifications at the aminosugar groups of aminoglycosides are being investigated to obtain novel antibiotics to overcome resistance. Plazomicin (62), derived through different modifications at N-6′, N-1, and N-3′ positions of N-3′ kanamycin A have proved to be less susceptible to aminoglycoside modifying enzymes having activity against the clinical isolates.\textsuperscript{74} Structural modifications of sugar moieties of macrolides are also under investigation to understand their therapeutic roles and antimicrobial resistance pattern. Myers \textit{et al.} (2021) reported that small alkyl amine group substitution at 6′ position of desosamine moiety of azithromycin like 15-membered macrolides (63, 64) exhibited potent activity.\textsuperscript{75} But these structure activity relationships have to be further investigated to come up with antibiotics that will be clinically effective. The desosamine sugar moiety of macrolides is essential for its interaction with bacterial ribosome.\textsuperscript{76} Macrolides with truncated desosamine moieties such as 2′-deoxymacrolides and 3′-desmethylmacrolides have reduced antibacterial activity.\textsuperscript{76} Condensation of another desosamine moiety at 4″- OH of clarithromycin with 11,12-arylalkyl side chains yielded products (65, 66) with better activities against resistant pathogens.\textsuperscript{77} Sugar moiety of the antifungal agents amphotericin B (67) and nystatin (68) known as mycosamine has gained considerable interest for modification to improve pharmacological activity and as well as to reduce toxicity. Bisalkylation of mycosamine sugar moiety of these two drugs yielded compounds (69, 70) with greater antifungal activity and less hemotoxicity.\textsuperscript{78} Compound 69 had MIC of 0.020µM whereas amphotericin B had 0.30µM and compound 70 exhibited MIC of 0.050µM compared to 3.0µM of nystatin.

A number of sugar esters have been investigated for antimicrobial activity.\textsuperscript{79-85} Alfindee \textit{et al.} (2018) identified 6-O-myristoyl-D-mannopyranose (71) as potential lead for development as antibacterial and antifungal agent.\textsuperscript{79} Jumina \textit{et al.} (2019) evaluated antibacterial and antifungal activities of synthesized myristate esters of fructose, glucose and galactose \textit{in vitro}. All the compounds showed notable activity against \textit{Candida albicans} of which fructosyl monomyristate (72) had highest zone of inhibition.\textsuperscript{80} Different esters of mannopyranoside and glucopyranoside for antibacterial and antifungal activity have been studied. Compound 73 exhibited 61.1% inhibition of fungal mycelial growth of \textit{Aspergilla flavus} which was more than that of fluconazole (47.0%).\textsuperscript{81} Compound 74 had
significantly higher inhibition of mycelial growth of *A. flavus* (69.20%) and *A. niger* (67.70%) compared to nystatin (12% and 16%, respectively). Compound 75—a novel ester of mannoypuranoside showed potent activity against *A. fumigatus* and *A. niger*. Ester of glucopyranoside compound 76 had considerable activity against four fungal species i.e. *A. fumigatus, A. niger, C. albicans* and *Fusarium solani*. Campana et al. (2019) also synthesized sugar based esters of where mannose capric acid ester 77 showed 97% inhibition of *Escherichia coli*. Disaccharide esters such as sucrose esters have also been studied for antimicrobial activity. Petrova et al. (2017) examined several sucrose esters of which compound 78 had the most potent antifungal activity studied over eight fungal species with the minimum inhibitory concentration ranging from (0.28-1.10µM).

Sugar based isoquinoline, naphthoquinone and their halogenated derivatives were investigated for antibacterial activity. Among the synthesized compound, compound 79 exhibited a MIC of 4µg/ml for *Pseudomonas aeruginosa* which was lesser than the MIC of corresponding naphthoquinone alone (8µg/ml). Several derivatives of 3-acetylcoumarin with sugar moiety thiosemicarbazones showed antibacterial activity against different gram-positive and gram-negative species with the MIC range of 0.78-12.5µM. From these compounds, compound 80 showed notable activity against three fungal species i.e. *A. flavus, A. niger* and *Saccharomyces cerevisae*. 1, 2, 3-Sucrose triazole derivatives also exerted in vitro antimicrobial activity against several bacterial and fungal species, among which compounds 81 and 82 had the highest antibacterial and antifungal activity with MIC range of 1.10-4.40µM and 0.60-4.80µM respectively.

**DISCUSSION**

From the above discussions it is evident that sugar and sugar derivatives possess diverse biological activity where the sugar moiety is essential for the exertion of desired pharmacological action. Again, modification of sugar moiety of drugs remains as an important area for developing more potent drugs than the parent compound during study of structure activity relationship. However, sugar moiety also plays important role in improving pharmacokinetic parameters of drugs and synthetic compounds. The classic example is of the glycosides in which the sugars are responsible for enhancing the hydrophilicity of aglycone moiety regardless of their role in the biological activity. Hydrophilicity and solubility have influences on other pharmacokinetic parameters such as absorption, distribution, bioavailability and elimination. Glycosylation has been used as an efficient method for modifying the physicochemical properties of therapeutically used peptides to achieve greater bioavailability. Paclitaxel which is widely used as chemotherapeutic agent suffers the problem of poor solubility and target specificity. Polyethoxylated castor oil surfactant is used to improve its solubility but this surfactant is toxic which leads to side effects. Single glucose and double glucose conjugated paclitaxel prodrug have been synthesized which resulted in increased release of the drug into blood as well as reduced toxicity against normal breast cells. Therefore, sugar and sugar derivatives are important members not as potential source of drugs but also as tools for drug development.

**CONCLUSION**

 Sugars and sugar derivatives have used therapeutically for several disorders. Both natural and synthetic derivatives have been found to exhibit potential pharmacological activities. Structural modifications of sugar moieties of existing drugs can also give rise to analogues with potent activity. This review represents the biological or pharmacological properties of various sugar derivatives developed in the last decade. Several interesting derivatives were reported by different groups and their reported pharmacological activities along with their available structure activity relationship data are presented here. This review might help the researchers in this field to find a credible lead for the new drug development based on sugar derivatives.
REFERENCES


A Review on Biological Activities of Sugar


