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REVIEW ARTICLE

Glycosides from Medicinal Plants as Potential Anticancer Agents: Emerging Trends Towards Future Drugs

Haroon Khan[1,*], Mina Saeedi[2,3], Seyed Mohammad Nabavi[4], Mohammad S. Mubarak[5] and Anupam Bishayee[6,*]

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ARTICLE HISTORY

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Abstract: ***Background*:** Cancer continues to be a global burden, despite the advancement of various technological and pharmaceutical improvements over the past two decades. Methods for treating cancer include surgery, radiotherapy and chemotherapy in addition to other specialized techniques. On the other hand, medicinal plants have been traditionally employed either as the complementary medicine or dietary agents in the treatment and management of cancer. Medicinal plants are a rich source of secondary metabolites with interesting biological and pharmacological activities. Among these metabolites, glycosides are naturally occurring substances and have outstanding therapeutic potential and clinical utility.

***Methods*:** Different medical research engines such as, GoogleScholar, PubMed, SpringerLink, ScienceDirect were used to collect related literature on the subject matter. In this regard, only peer-reviewed journals were considered.

***Results*:** Emerging results showed that numerous glycosides isolated from various plants possessed marked anticancer activity against a variety of cancer cell lines. Accordingly, the aim of the present review is to shed light on the anticancer effects of glycosides, analyze possible mechanisms of action, and highlight the role of these natural agents as complementary and alternative medicine in combating and managing cancer.

***Conclusion*:** The glycosides isolated from different plants demonstrated potent cytotoxic effects against various cancer cell lines in initial preclinical studies. The anticancer effect was mediated through multiple mechanisms; however further detailed studies are needed to understand the full potential of glycosides for clinical utility.

Keywords: Anticancer agents, glycosides, medicinal plants, derivatives, safety parameter, drugs of future.

1. INTRODUCTION

Cancer continues to be among the most feared of human diseases. It is recognized as a major threat to health since the earliest days of documented history [1]. It is considered as an adversary of modernization and the pattern of socio-economical life dominated by Western medicine. Cancer is still considered one of the most frequent causes of human fatality, particularly in technologically-advanced countries. In these countries, it accounts for about 15 to 20% of deaths each year [2, 3]. One important strategy in combating cancer is chemoprevention, a method of cancer control by pharmacological intervention with chemical compounds. Recent events suggest that new emphasis has been given to research on complementary and alternative medicine that deals with cancer management [4-6].

The use of medicinal plants in modern medicine for the prevention and treatment of cancer is central in combating the disease. For this reason, it is of paramount importance to identify anticarcinogenic agents present in medicinal plants which can inhibit the initia-

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tion, promotion and progression of tumor [7-9]. Medicinal plants and their endophytes are important resources for the discovery of clinically-relevant natural products [10-12]. They are also incorporated into ancient folk medicine of virtually all human cultures. Additionally, these plants are a rich source of secondary metabolites with interesting biological activities; these secondary metabolites have a variety of structural arrangements and properties [13].

Glycosides are organic compounds derived or extracted from plant or animal sources. Upon enzymatic or acid hydrolysis, these compounds give one or more sugar moieties along with a non-sugar residue. The sugar moiety is described as a glycone, whereas the non-sugar part is called aglycone or genin. Chemically, these glycosides are acetals or sugar ethers formed by the interaction of hydroxyl groups of the non-sugar and sugar moieties with a loss of a water molecule [14, 15]. There are four glycosidic linkages including S-, N-, C-, and O-glycosidic bonds indicating connecting atoms between anomeric carbon of glycone and that of aglycone. Among them, C-glycosyl structures are usually more resistant to hydrolysis.

This review focuses on the role played by natural glycosides as potential anticancer agents, critically analyzes the possible mechanisms of action, and highlights the role of these natural agents as complementary and alternative medicine in combating and managing cancer.

2. STEREOCHEMISTRY OF GLYCOSIDES

It is well-known that sugars are available in two acyclic and cyclic forms leading to the formation of L/D and α/β stereoisomers, respectively. L and D configurations are described by the position of hydroxyl group connected to the asymmetric carbon furthest from carbonyl group in the Fischer projection in which OH is placed on the left or right side, respectively. α/β anomers are determined by the position of substituents connected to anomeric carbon in the cyclized form. In this regard, glycosides are categorized into α -glycosides and β-glycosides depending on the position of glycosidic bond whether it is positioned below or above the plane of glycone [16].

The biological activity of glycosides are directly affected by their stereochemistry; hence, their stereoselective preparation is highly in demand [17]. Most of the naturally occurring glycosides such as digoxin and digitoxin possess β-D stereochemistry. However, there are a few exceptions, such as ouabain having α -L stereochemistry which is very potent cardiac glycoside. It is worth mentioning that appropriate stereoisomers of cardiac glycosides play a remarkable role in binding to the Na^+, K^+-ATPase receptor to promote cardiac muscle contraction [18, 19]. In this respect, digitoxin, digoxin and ouabain have shown desirable biological activities [18].

Recently, the anticancer activity of glycosides, especially ouabain, digoxin, digitoxin, digitoxigenin, and lanatoside C, has attracted lots of attention not only due to an increase of solubility and distribution in the body resulting from sugar moiety but also due to the effect of the stereochemistry of sugar moiety on binding affinity to the receptor protein. The study reported by Thorson *et al*. [20] revealed that the anticancer properties of cardiac glycosides could be improved by the modification of stereochemistry of sugar moieties. Also, various research groups have explored the best alignment of OH of ginsenoside Rg3 epimers with that of the OH acceptor group to induce better anticancer activity confirming the significance of stereochemical characteristics of the glycone moiety [21, 22].

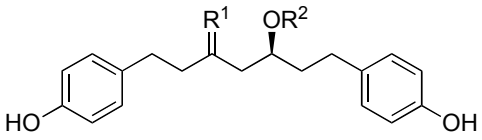
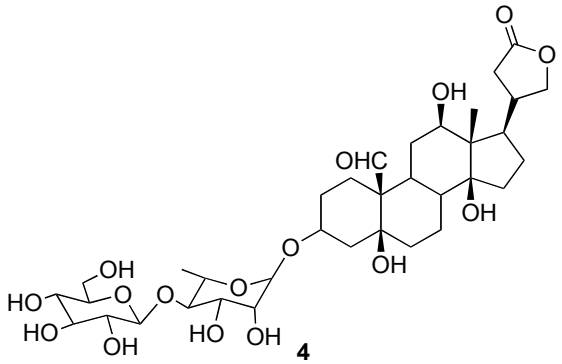
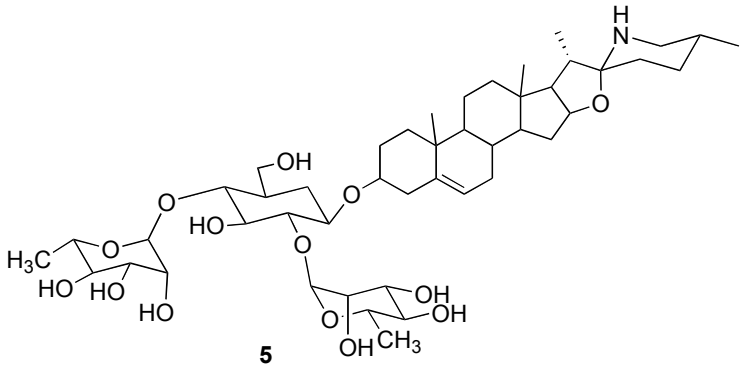
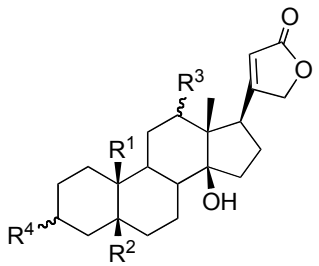
3. GLYCOSIDES AS THERAPEUTIC AGENTS

There are different types of glycosides, such as triterpene, β -sitosterol, flavonoid, iridoid, phenylpropanoid, anthraquinone, kaempferol, and saponine glycosides. In the saponine glycoside, the aglycone part is referred to as a sapogenin, whereas the glycone parts are generally oligosaccharides [23, 24]. Oligosaccharides may be linked to sapogenin *via* an ether or ester linkage at one or two glycosylation sites, giving the corresponding monodesmosidic or bidesmosidic saponins, respectively. However, attachment of the glycone to three sites (tridesmosidic) in a sapogenin is rare [25, 26]. While considering the dazzling history of glycosides as therapeutic agents, the current review is focused on the anticancer potential of glycosides derived from plants, proposed mechanism and possibility of use as future drugs for the treatment of various cancers.

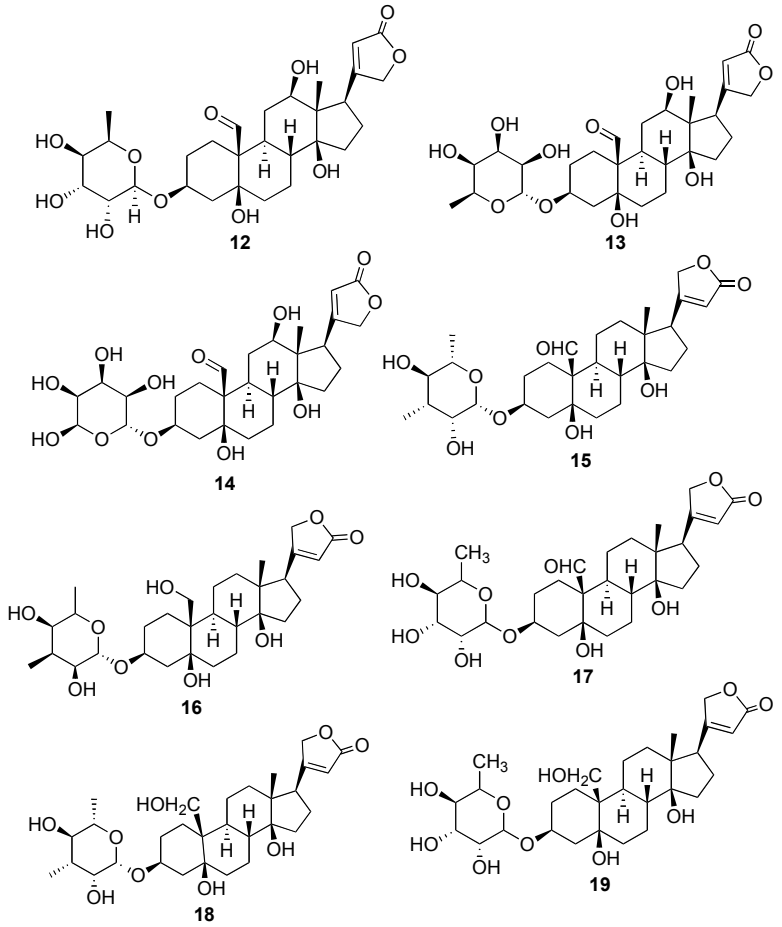
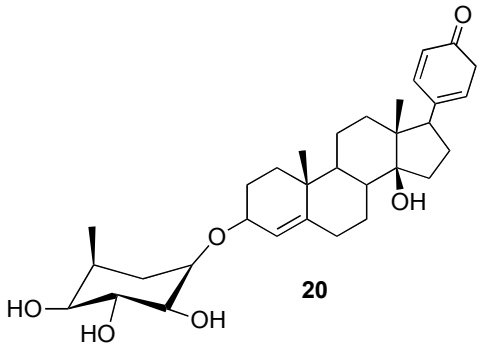
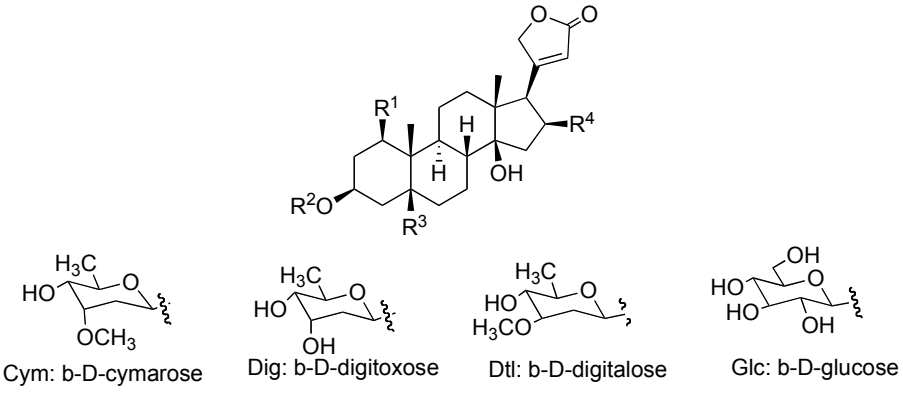
4. GLYCOSIDES AS AN ANTICANCER AGENT

A Canadian research group isolated several glycosides from of *Betula papyrifera* bark [27]. These diarylheptanoid glycosides, namely papyriferoside A **1**, 5-O-β-D-apiofuranosyl-(1→2)-β-D-glucopyranosyl-1, 7-bis-(4-hydroxyphenyl)-heptan-3-one **2,** and platyphyl loside **3** (Table **1**), showed marked cytotoxicity when studied in an *in vitro* assay against various cancer cell lines, including lung carcinoma, colorectal adenocarcinoma, and normal skin fibroblast with IC_{50} values in the range of 10.3-13.8 μM.

Table 1. Isolated plant isolated glycosides with anticancer activity.

Plant Name	Chemical Structure of Isolated Compound	Refs.
Betula papyrifera	 R1 R2 **1** O α-L-Araf-[1→6]-β-D-Glcp **2** O β-D-Api-[1→2]-β-D-Glcp **3** H_2 β-D-Glcp	[27, 84]
Antiaris toxicaria	 **4**	[28, 30]
Solanum incanum	 **5**	[85, 86]
Antiaris toxicaria	 R1 R2 R3 R4 **6** CHO OH β-OH β-O-4,6-dideoxy-β-D-allose **7** CHO OH α-OH β-O-α-L-rhamnose **8** CHO H β-OH β-O-6-deoxy-β-D-glucose **9** CHO H β-OH β-O-6-deoxy-β-D-allose **10** CHO H β-OH β-O-α-L-rhamnose **11** CH_2OH H β-OH β-O-6-deoxy-β-D-glucose	[30, 87]

(Table 1). contd…..

Plant Name	Chemical Structure of Isolated Compound	Refs.
		
Urginea maritima		[33, 88]
Streptocaulon juventas		[34, 89]

(Table 1). contd…..

Plant Name	Chemical Structure of Isolated Compound					Refs.
	Compound	R^1	R_2	R_3	R^4	
	16-O-Acetyl-hydroxyacovenosigenin 21	β-OH	H	H	OAc	
	6-O-acetylhydroxyperiplogenin 3-O-β-D-digitoxopyranoside 22	H	Dig	OH	OAc	
	14β-dihydroxy-5β-card-20 (22)-enolide 3-O-[O-β-D-glucopyranosyl-(1→2)-β-D-digitalopyranoside] 23	α-OH	Dtl^2-Glc	H	H	
	Acovenosigenin A3-O-[O-β-D-glucopyranosyl-(1 →4)-β-D-digitalopyranoside]24	β-OH	Dtl^4-Glc	H	H	
	Acovenosigenin A 25	β-OH	H	H	H	
	acovenosigenin A β-glucoside 26	β-OH	Glc	H	H	
	acovenosigenin A 3-O-β-digitoxopyranoside 27	β-OH	Dig	H	H	
	Evonogenin 28	β-OH	H	OH	H	
	Glucoevonogenin 29	β-OH	Glc	OH	H	
	5β-hydroxygitoxigenin 30	H	H	OH	OH	
	16-Oacetyl-hydroxyperiplogenin 31	H	H	OH	OAc	
	Oleandrigenin 32	H	H	H	OAc	
	Subapinoside 33	H	Dig^4-Glc	H	OAc	
	Honghelotrioside A 34	H	Cym^4-Glc^6-Glc	H	OAc	
	Glucogitoroside 35	H	Dig^4-Glc	H	OH	
	digitoxigenin 3-O-[O-β-D-glucopyranosyl-(1 →4)-2-O-acetyl-β-D-digitalopyranoside] 36	H	$(2\text{-O-Ac-Dtl})^4$-Glc	H	H	
	digitoxigenin 3-O-[O-β-D-glucopyranosyl-(1→6)-O-β-D-glucopyranosyl-(1 →4)-2-O-acetyl-β-D-digitalopyranoside] 37	H	$(2\text{-O-Ac-Dtl})^4$-Glc^6-Glc	H	H	
	Digitoxigenin 38	H	H	H	H	
	Acetodigin 39	H	Glc	H	H	
	honghelosid G 40	H	Cym	H	H	
	Glucoevatromonoside 41	H	Dig^4-Glc	H	H	
	Echunbioside 42	H	Cym^4-Glc	H	H	
	digitoxigenin gentiobioside 43	H	Glc^6-Glc	H	H	
	digitoxigenin 3-O-[O-β-D-glucopyranosyl-(1→4)-β-D-glucoside] 44	H	Glc^4-Glc	H	H	
	digitoxigenin sophoroside 45	H	Glc^2-Glc	H	H	
	digitoxigenin 3-O-[O-β-D-glucosyl-(1→4)-3-O-acetyl-β-D-digitoxoside] 46	H	$(3\text{-O-Ac-Dig})^4$-Glc	H	H	
	Echujin 47	H	Cym^4-Glc^6-Glc	H	H	

(Table 1). contd…..

<table>
<tr><th>Plant Name</th><th>Chemical Structure of Isolated Compound</th><th>Refs.</th></tr>
<tr><td></td><td>
<table>
<tr><td>digitoxigenin 3-O-[O-β-glucopyranosyl-(1 →6)-O-β-glucopyranosyl-(1 →4)-3-O-acetyl-β-digitoxopyranoside] 48</td><td>H</td><td>(3-O-Ac-Dig)^4-Glc^6-Glc</td><td>H</td><td>H</td></tr>
<tr><td>digitoxigenin 3-O-β-gentiobiosyl-(1 →4)-O-β-D-digitoxopyranoside 49</td><td>H</td><td>Dig^4-Glc^6-Glc</td><td>H</td><td>H</td></tr>
<tr><td>digitoxigenin 3-O-[O-β-glucopyranosyl-(1→6)-O-β-glucopyranosyl-(1→4)-O-β-digitalopyranosyl-(1 →4)-β-cymaropyranoside] 50</td><td>H</td><td>Cym^4-Dtl^4-Glc^6-Glc</td><td>H</td><td>H</td></tr>
<tr><td>Odoroside G 51</td><td>H</td><td>Dtl^4-Glc^6-Glc</td><td>H</td><td>H</td></tr>
<tr><td>periplogenin 3-O-[O-β-D-glucopyranosyl-(1 →4)-O-β-Dglucopyranosyl-(1 →4)-β-D-cymaropyranoside] 52</td><td>H</td><td>Cym^4-Glc^4-Glc</td><td>OH</td><td>H</td></tr>
<tr><td>Periplogenin 53</td><td>H</td><td>H</td><td>OH</td><td>H</td></tr>
<tr><td>Periplogenin glucoside 54</td><td>H</td><td>Glc</td><td>OH</td><td>H</td></tr>
<tr><td>Emicymarin 55</td><td>H</td><td>Dtl</td><td>OH</td><td></td></tr>
<tr><td>Periplogenin 3-O-β-digitoxoside 56</td><td>H</td><td>Dig</td><td>OH</td><td>H</td></tr>
<tr><td>Periplogenin 3-O-β-glucopyranosyl-(1 →4)-O-β-digitaloxopyranoside 57</td><td>H</td><td>Dtl^4-Glc</td><td>OH</td><td>H</td></tr>
<tr><td>Corchorusoside C 58</td><td>H</td><td>Dig^4-Glc</td><td>OH</td><td>H</td></tr>
<tr><td>Periplocymarin 59</td><td>H</td><td>Cym</td><td>OH</td><td>H</td></tr>
<tr><td>Biondianoside A 60</td><td>H</td><td>Cym^4-Glc^6-Glc</td><td>OH</td><td>H</td></tr>
<tr><td>1β,3β,14β-trihydroxy-5β-c rd-16, 20 (22)- dienolide 61</td><td>β-OH</td><td></td><td>H</td><td>$\Delta^{16,17}$</td></tr>
<tr><td>Griffithigenin 62</td><td>H</td><td>H</td><td>OH</td><td>$\Delta^{16,17}$</td></tr>
<tr><td>Δ(16)-digitoxigeninβ-D-glucoside 63</td><td>H</td><td>Glc</td><td>H</td><td>$\Delta^{16,17}$</td></tr>
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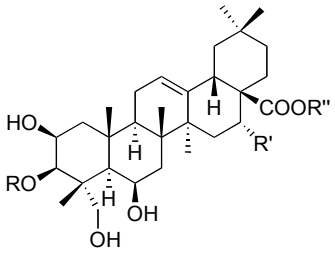
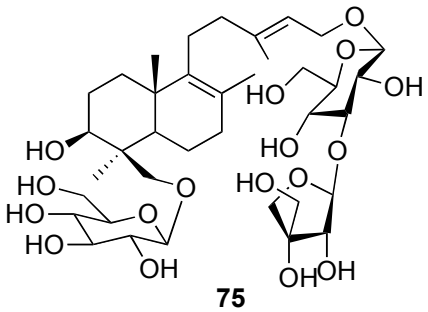
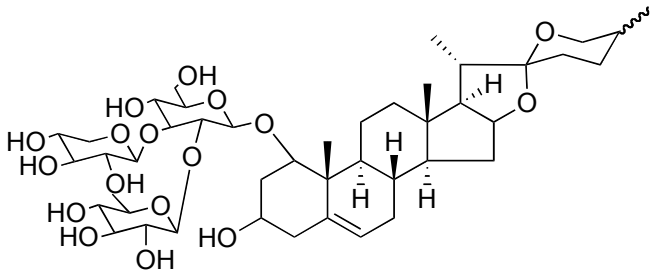
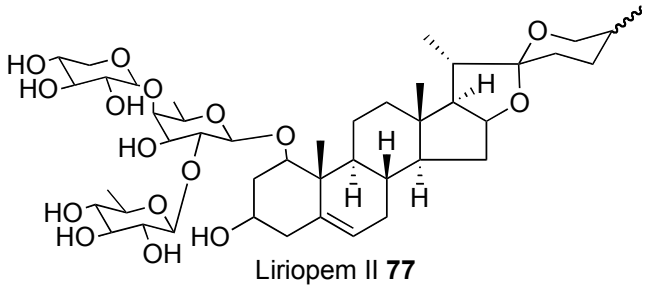
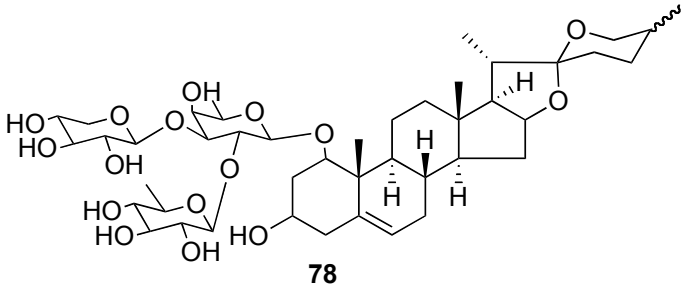
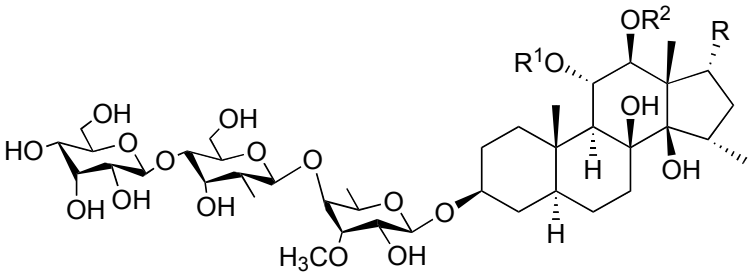
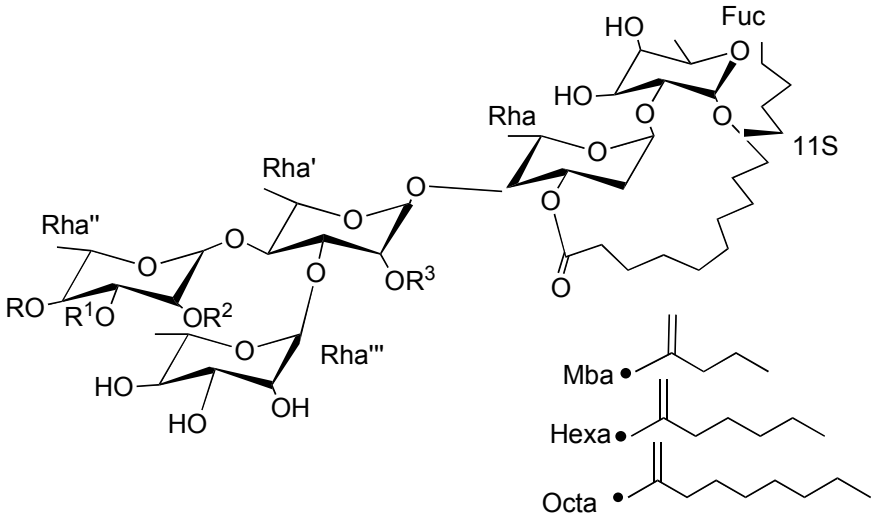
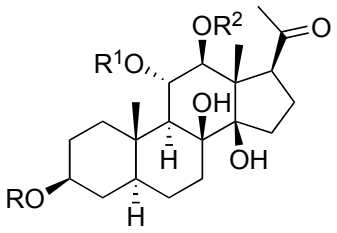
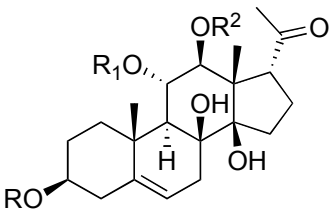
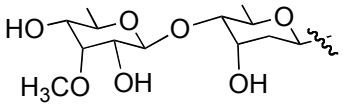
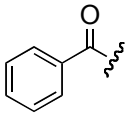
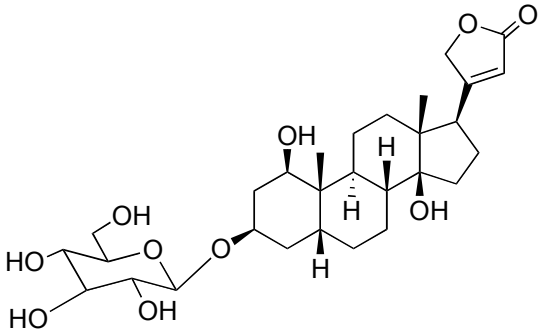
</td></tr>
<tr><td>Vitellaria paradoxa</td><td>


<table>
<tr><th></th><th>R</th><th>R'</th><th>R"</th></tr>
<tr><td>Paradoxoside A 64</td><td>GlcA</td><td>OH</td><td>Rha-(1→2)-Ara</td></tr>
<tr><td>Paradoxoside B 65</td><td>GlcA</td><td>OH</td><td>Xyl-(1→4)-Rha-(1→2)-Ara-</td></tr>
<tr><td>Tieghemelin A 66</td><td>GlcA</td><td>OH</td><td>Rha-(1→3)-Xyl-(1→2)-Rha-(1→2)-Ara-</td></tr>
<tr><td>Butyroside D 67</td><td>GlcA</td><td>OH</td><td>Api-(1→3)-Xyl-(1→2)-Rha-(1→2)-Ara-</td></tr>
<tr><td>Arginine C 68</td><td>Glc</td><td>OH</td><td>Rha-(1→3)-Xyl-(1→2)-Rha-(1→2)-Ara-</td></tr>
<tr><td>3-O-β-D-glucuronopyranosyl 16α-hydroxyprotobassic acid 69</td><td>GlcA</td><td>OH</td><td></td></tr>
<tr><td>3-O-β-D-glucopyranosyl 16α-hydroxyprotobassic acid 70</td><td>Glc</td><td>OH</td><td></td></tr>
<tr><td>Paradoxoside C 71</td><td>MeGlcA</td><td>H</td><td>H</td></tr>
<tr><td>Paradoxoside D 72</td><td>Glc-(1→3)-Glc</td><td>H</td><td>H</td></tr>
<tr><td>3-O-β-D-glucuronopyranosyl protobassic acid 73</td><td>GlcA</td><td>H</td><td>H</td></tr>
<tr><td>Mi-glycoside I 74</td><td>Glc</td><td>H</td><td>H</td></tr>
</table>
</td><td>[35, 90]</td></tr>
</table>

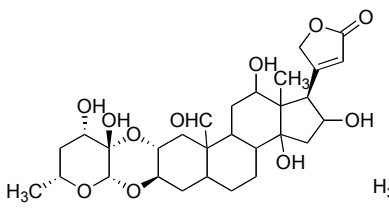
(Table 1). contd…..

Plant Name	Chemical Structure of Isolated Compound	Refs.
Rubus chingii	 **75**	[36, 91]
Liriope muscari	 Liriopem I **76**  Liriopem II **77**  **78** Ruscogenin-1-O-[b-D-glucopyranosyl-(1→2)]-[b-D-xylopyranosyl-(1→3)]-b-Dfucopyranoside.	[37, 92]
Desmidorchis flava		[38, 93]

(Table 1). contd…..

Plant Name	Chemical Structure of Isolated Compound	Refs.
Ipomoea aquatica	 Aquaterin XII **80** = R: Octa, R^1: H, R^2: Octa, R^3: Mba Aquaterin XIII **81** = R: Octa, R^1: Octa, R^2: H, R^3: Mba Aquaterin XV **82** = R: Octa, R^1: H, R^2: Octa, R^3: Hexa	[39, 94]
Dregea sinensis	 **83** R= Ra; R^1 = R^2 = Bz  **84** R= Ra; R^1 = R2 = Bz Ra =  Bz= 	[40, 95]
Streptocaulon juventas	 **85**	[41, 96]

(Table 1). contd…..

<table>
<tr><th>Plant Name</th><th>Chemical Structure of Isolated Compound</th><th>Refs.</th></tr>
<tr><td>Asclepias subulata</td><td> 
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 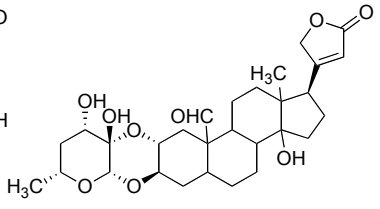
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 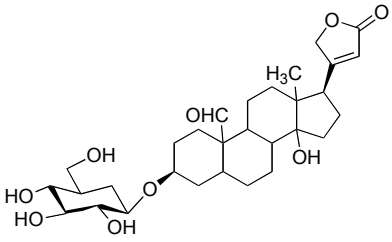
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 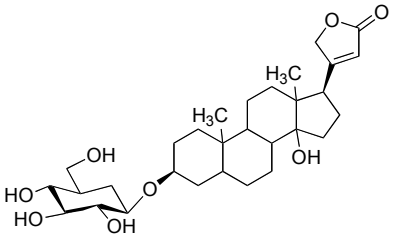
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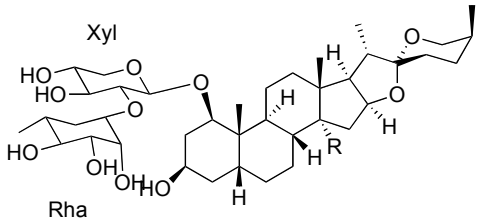
<tr><td>Reineckia carnea</td><td> 
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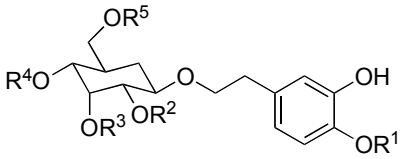
<tr><td>Magnolia officinalis</td><td> 
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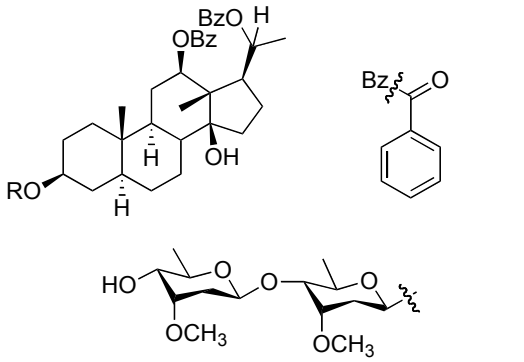
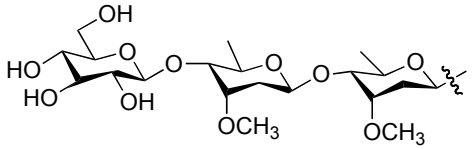
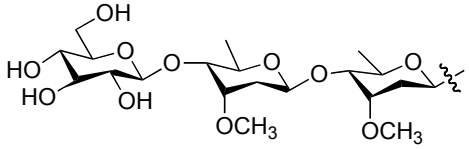
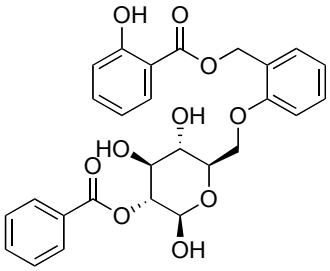
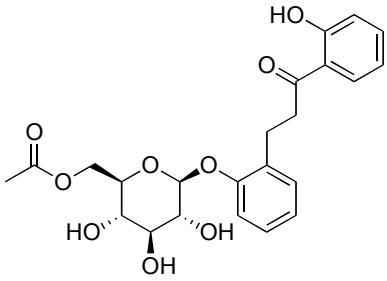
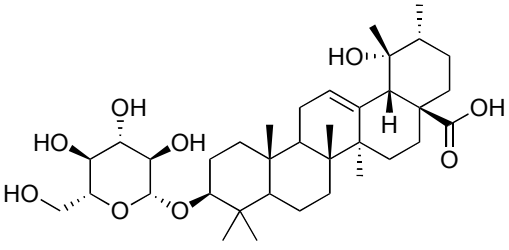
</table>

(Table 1). contd…..

Plant Name	Chemical Structure of Isolated Compound	Refs.
Desmidorchis flava	 R = Desmiflavasides C **106**  R = Desmiflavasides D **107**  R = Nizwaside D **108**	[100, 101]
Salix acmophylla	 Acmophyllin A **109**  Acmophyllin B **110**	[47, 102]
Wedelia calendulacea	 **111**	[48, 103]

Gan *et al*. [28] isolated a toxicarioside E **4** from *Antiaris toxicaria*. This cardenolide glycoside illustrated marked cytotoxicity against human cancer cell lines, chronic myelogenous leukemia and human gastric cancer cells with IC_{50} values of 0.026 and 0.027 μg/mL, respectively. Sun and Colleagues [29] studied the anticancer profile of steroidal glycoside, solamargine **5**, isolated from *Solanum incanum* in several cancer cells. It showed marked anticancer effects in multiple cancer cells, including multiple-drug-resistant cancer cells.

Liu and colleagues [30] isolated a number of glycosides from *Antiaris toxicaria*. Of them, antiaroside J **6,** antiaroside N **7,** antiaroside O **8,** antiaroside P **9,** antiaroside Q **10,** antiaroside X **11,** ß-antiarin **12**, antialloside **13**, toxicarioside B **14**, convallatoxin **15**, strophalloside **16**, desglucocheirotoxin **17**, convallatoxol **18** and deglucocheirotoxol **19** showed marked anticancer action when tested against human NIH-H460 lung cancer cells. The structure-activity relationship of these compounds revealed that the orientation of C-3 and C-17 substituents played an important role in the overall cytotoxic profile. On the other hand, the compounds which α-oriented at C-3 and C-17 substituents showed weak anticancer effects [20]. Similarly, compounds contained α-L-rhamnose moiety at C-3 exhibited potent cytotoxic activities [31]. For cytotoxicity, the position of glycone linkage is also very crucial. For instance, compounds in which the sugar was attached to C-19 showed poor cytotoxicity than those in which this moiety was linked to C-3 [30, 32].

During the anticancer study of Egyptian medicinal plants based on traditional uses, total 61 plants were tested which led to the isolation of a cardiac glycoside, proscillaridin A **20** from *Urginea maritima* [33]. It showed significant cytotoxicity against lymphoma cell line at various test concentrations. The researchers from Shenyang Pharmaceutical University (Shenyang, Liaoning, China) isolated 43 cardiac glycosides using *Streptocaulon juventas* roots [34]. These glycosides **21-63** exhibited varying degree of cytotoxicity against various human lung cancer cell lines.

A multicentre study of Zhang *et al*. [35] isolated a number of compounds from *Vitellaria paradoxa* in which glycosides **64-74** when tested for anticancer effect, they showed marked cytotoxicity and antitumor effects. When these cardiac glycosides **64-74** were tested for anticancer effect, they showed marked activity lungs cancer cell line *in vitro*. The SAR studies in these compounds showed that the monodesmosides glycosylated at C-3 proved to be more potent cytotoxic.

In 2015, a Chinese group of researchers phytochemically investigated *Rubus chingii* for secondary metabolites which led to the isolation of three new glycosides [36]. These compounds were screened against five different human cancer cell lines in which only 5-O-β-D-apiofuranosyl-(1→2)-β-D-glucopyranosyl-18-O-β-D-glucopyranosyl-13(E)-ent-labda-8(9),13(14)-diene 3β,15,18-triol **75** showed potent cytotoxicities against human lung cancer cell lines (IC_{50}: 2.32 μM). Li and co-workers [37] derived steroidal glycosides **76-78** from *Liriope muscari*. These glycosides exhibited an outstanding anticancer activity against human breast cancer lines with IC_{50} values of 0.58, 0.05 and 0.15 μg/ml. The phytochemical investigation on *Desmidorchis flava* led to the isolation of pregnane glycosides [38]. Out of which, desmiflavasides B **79** showed concentration-dependent anticancer activity against breast cancer cell line.

Fan *et al*. [39] isolated several glycosides from water spinach (*Ipomoea aquatica*). These compounds were analyzed against six different cancer cell lines and compounds **80-82** showed marked *in vitro* cytotoxicity. Jia *et al*. [40] isolated six glycosides from *Dregea sinensis*. Out of them, only **83** and **84** showed cytotoxicity towards human leukemia cells (HL-60) with IC_{50} values of 14.10 μM and 19.16 μM, respectively. Similarly, Xue *et al*. [41] isolated TXA9 from *Streptocaulon Juventas* and tested for anticancer activity in both *in vivo* and *in vitro* experiments. The results showed marked cytotoxic effect on lungs cancer lines *in vitro*. Similarly, the *in vivo* treatment of mice with TXA9 at 15 mg/kg caused profound antitumor effect (64.2%). Similarly, the bioactivity-guided isolation on *Asclepias subulata* led to the cardenolide glycosides **86-89** [42]. When these were tested for anticancer activity against various cancer cell line, outstanding potencies were observed with IC_{50} in the range of 0.0013-6.99 μM.

The isolated labdane-type diterpene glycosides were tested against various human cell lines. Of the tested cell lines, 15-O-β-D-apiofuranosyl-(1→2)-β-D-glucopyranosyl-18-O-β-D-glucopyranosyl-13(E)-ent-labda-8(9),13(14)-diene-3β,15,18-triol showed marked cytotoxic effect against A549 cells with IC_{50} values of 2.32 μM. Similarly, researcher isolated 14 glycosides from *Ixeris dentata* roots [43]. These sesquiterpene lactone glycosides when tested for cytotoxicity, but no significant effect was observed. Zheng and colleagues [44] isolated five compounds from *Reineckia carnea* roots. These steroidal glycosides when studied for possible cytotoxicity against Caski cancer cell line, compounds 25(S)-5β-spirostan-1β,3β,14β-triol-1-O-α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranoside **90** and 25(S)-5β-spirostan-1β,3β-diol-1-O-α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranoside **91** showed prominent cytotoxicity with IC_{50} values of 34.4 and 3.7μM, respectively. Similarly, Xue *et al*. [45] isolated 26 glycosides from *Magnolia officinalis* stem bark. Of the various human cancer cell lines used in the assay, compounds **92-105** showed cytotoxicity against MGC-803 and HepG2 cells.

Raees and co-workers [46] isolated three pregnane glycosides from *Desmidorchis flava*. When these iso-

lated glycosides **106-108** were tested against breast cancer and ovarian cancer cell lines, marked cytotoxicity observed with IC_{50} values of 19.97-25.84 μM and 37.97-64.5 μM, respectively. Recently, a Pakistani research group [47] isolated two salicin glycosides acmophyllin A and acmophyllin B from *Salix acmophylla* leaves. These compounds were tested for anticancer activity against various cancer cell line, including pancreatic, breast and lung, where they showed encouraging activity. Most recent studies of Verma and coworkers [48] isolated and characterized a novel glycoside from *Wedelia calendulacea* named as 19-α-hydroxy-ursolic acid glucoside [19-ahydroxyurs-12(13)-ene-28 oic acid-3-O-β-D-glucopyranoside **111**. Treatment of rats with this compound produced significant inhibition of renal tumor by down-regulation of ornithine decarboxylase.

5. ANTICANCER MECHANISM OF ACTION

Extensive research on the mechanistic insights has explored almost every aspect of anticancer agents [49-51]. Cardiac glycosides (CGs) are compounds used for the treatment of cardiac failure. Additionally, they possess strong anticancer activity and induce impairment of cell proliferation or activation of cell death by apoptosis or autophagy. CGs may also induce autophagic-like cell death. Mcl-1 has been recently discovered to sequester Beclin-1, an important mediator of autophagy in neuronal cell models, and its degradation is an event strictly required to allow onset of autophagy. Therefore, Mcl-1 degradation may lead to apoptosis or to autophagic cell death [52]. Research showed that the glycoalkaloid solamargine (SM) significantly inhibits the growth of human hepatoma SMMC-7721 and HepG2 cells and induces cell apoptosis. In addition, SM causes cell cycle arrest at the G_2/M phase and upregulates the expression of caspase-3 [53]. The effect of CO-OCS and SO-OCS is triggered by both cell cycle arrest and apoptosis, showing that these castanospermine analogues may be used as potential anticancer agents against breast cancer [54]. The anticancer effects for cardiac glycosides isolated from *Antiaris toxicaria* were found to be in conjunction with induction of Nur77 protein expression [30, 55].

Amygdalin can induce apoptosis in human promyelocytic leukemia (HL‐60) cells. Amygdalin suppressed the proliferation of human colon cancer SNU‐C4 cell through the mechanism that involves inhibition of expression of cell cycle related genes. Furthermore, amygdalincan induced apoptosis in DU145 and LNCaP prostate cancer cells by regulating the expression of Bax and Bcl‐2, and inhibited the survival of HeLa cells in a concentration-dependent manner [56]. In a similar fashion, reevesioside A inhibited c-myc expression and down-regulated the expression of CDC25A, cyclin D1 and cyclin E, leading to a profound decrease of RB phosphorylation. G_1 arrest is, therefore, induced through E2F1 suppression. Consequently, reevesioside A caused mitochondrial damage and apoptosis in human hormone-refractory prostate cancer cells [57].

Four cardenolide glycosides with strong antiproliferative activity were isolated from *Asclepias subulata*: one new, namely 12,16-dihydroxycalotropin, and three known compounds, such as scalotropin, corotoxigenin3-O-glucopyranoside, and desglucouzarin. The isolated cardenolide glycosides showed selectivity to human cancer cells. Results also revealed that *A. subulata* could be a potential source of anticancer agents with the underlying mechanism of apoptosis induction [58, 59]. In a similar fashion, aquaterin II induced G_0/G_1 arrest regulated by related proteins CDK4/6, cyclin D/E and p21, and caused mitochondria-mediated apoptosis featured by matrix metalloproteinase (MMP) decrease, reactive oxygen species (ROS) accumulation, caspase cascade activation, and Bax/Bcl-2 alteration. Additionally, suppression of the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway was observed, suggesting that it may be involved in aquaterin II-induced cell growth inhibition [60].

Triterpene glycosides are characteristic secondary metabolites of sea cucumbers. The anticancer molecular mechanisms of these compounds include: (a) induction of tumor cell apoptosis by the activation of intracellular caspase cell death pathways; (b) arrest of the cell cycle at S or G_2/M phases; (c) influence on the nuclear factor-κB (NF-κB); and (d) up- or down-regulation of certain cellular receptors and enzymes participating in carcinogenesis, such as epidermal growth factor receptor (EGFR)), Akt (protein kinase B), extracellular signal-regulated kinases (ERK), focal adhesion kinase (FAK), MMP-9 and others [61]. On the other hand, the methanolic leaf extract of *Olaxmannii* led to the isolation of 17 flavonoid glycosides, three of which were new compounds. One of the isolated compounds, kaempferol 3-O-α-L-rhamnopyranoside, was found to exhibit significant and selective cytotoxicity by the inhibition of NF-κB [62].

6. SYNTHETIC DERIVATIVES

In 2004, Popiolkiewicz and coworkers [63] synthesized genistein glycosides using genistein as a major soy isoflavone. The compounds were synthesized in the hope to encounter some of the intrinsic limitations and

improve pharmacokinetic parameters of parent compound which already demonstrated great potential as a lead compound in studies reported from different centers [64-67]. The synthesized compounds showed enhanced potencies than genistein, a soy-derived isoflavone and phytoestrogen with anticancer activity, as well as better pharmacokinetic profile. Similarly, the safety profile of these compounds was also studied in both *in vitro* and *in vivo* models to evaluate their clinical status. The results revealed marked the safety of these compounds in comparison to clinically used chemotherapeutics [68].

Anand and colleagues [69] synthesized various cardiac glycoside. The purpose was the study of glycone part on their anticancer action. The anticancer effect was found to be sugar-dependent. Nitin and colleagues [70] synthesized a series of perillyl alcohol glycosides through a new facile route. When studied for antiproliferative effect, these compounds were found highly potent and the cytotoxic activity was glycone-dependent.

Podophyllotoxin is regarded as the most potent, versatile anticancer agents but never get clinical status due to several unwanted sides effects. However, some of its derivatives, etoposide and etopophos are in clinical uses [71-73]. Zi *et al*. [74] synthesized a number of perbutyrylated glycosides of podophyllotoxin. The overall effects of these compounds were outstanding against different cancer cell lines with IC_{50} values in the range of 0.14-1.69 μM. Interestingly, some the derivatives were found more potent than the standard drugs, etoposide and etopophos. Further, studies in this regard could lead to clinical application. The electron-withdrawing groups, such as F, Cl and NO_2 on phenyl ring, exhibited strong activity when compared to electron-donating such groups, such as OH and OCH_3 groups [75, 76].

The novel glycoside derived from *Wedelia calendulacea* caused inhibition of ornithine decarboxylase [48] which is considered as an important mediator of tumor proliferation [77, 78]. Additionally, the potent antioxidant property of the compound further augmented the antitumor effect as reported to an important promoter of tumor [79].

7. NOVEL EXTRACTION TECHNIQUES

Recently, different extraction techniques have been developed for extraction of various types of components [80]. Extraction is a primary step in the isolation of secondary metabolites. The pressurized hot water extraction technique are already reported for extraction [81, 82]. In this regard, Liau *et al*. [83] has designed a very significant pressurized hot water extraction technique coupled with HPLC/ESI-MS-MS for the isolation of flavonoid glycosides from *Camellia oleifera*. The latest development in extraction methodology and the involvement of HPLC, MS and ESI could play an important role in the standardized of crude formulations and identification of isolated compounds.

8. TOXICOLOGICAL PROFILE OF ANTICANCER GLYCOSIDES

In general, the isolated glycosidal compounds showed specific cytotoxic effects against various cancer cell lines. However, some exception has been reported with toxicity towards normal cells. The glycosides from *Betula papyrifera* **1-3** caused non-selective toxicity even toxic to normal cells [27]. Solamargine was less toxic to normal cells with IC_{50}: 23.4 μM [29]. TXA9 isolated from *S. juventas* roots when studied for potential toxicity in normal lungs cell line, and it was found to be absolutely safe [41]. It is also worth mentioning that in most of the cases the effect against normal cell lines have not been test, therefore, based on these results the untested glycosides also need to be studied for their activity towards normal cells in order to ascertain their clinical status.

CONCLUSION

Naturally-occurring glycosides are present in significant amounts in medicinal plants. Several of these glycosides possess anticancer activity. Glycosides extracted from medicinal plants have been recognized and employed as alternative drugs in treating different cancers. In this review, we demonstrate that natural glycosides provide a wide range of preventive and therapeutic options against different types of cancer either alone or in combination with other chemotherapeutic drugs. Additionally, these therapies based on phytochemicals could constitute a novel pharmacological approach for the treatment of cancer. This review has focused on the use of glycosides as chemopreventive and therapeutic agents along with a description of the various mechanisms by which these compounds exert their action. In conclusion, this review reveals that glycosides can be used in complementary medicine for the prevention and treatment of different types of cancers due to their natural origin, safety, and low-cost relative to available cancer drugs. However, further studies are needed on these natural compounds to understand the full potential of these compounds for their clinical utility.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES

[1] American Cancer Society. *Early history of cancer.* Available at: http://www.cancer.org/cancer/cancerbasics/ thehistoryofcancer/the-history-of-cancer-what-is-cancer2016.

[2] Surya, S.P.; Jayanthi, G.; Smitha, K.R. *In vitro* evaluation of the anticancer effect of methanolic extract of *Alstonia scholaris* leaves on mammary carcinoma. *J. Appl. Pharm. Sci.,* **2012**, *2*(5), 142-149.

[3] D'Incalci, M.; Galmarini, C.M. A review of trabectedin (ET-743): A unique mechanism of action. *Mol. Cancer Ther.,* **2010**, *9*(8), 2157-2163. [http://dx.doi.org/10.1158/1535-7163.MCT-10-0263] [PMID: 20647340]

[4] Patil, A.; Vadera, K.; Patil, D.; Phatak, A.; Juvekar, A.; Chandra, N. *In vitro* anticancer activity of *Argemone mexicana* L. seeds and *Alstonia scholaris (l.)* R. Br. bark on different human cancer cell lines. *World J. Pharm. Pharm. Sci.,* **2014**, *3*(11), 706-722.

[5] Jeremić, M.; Pešić, M.; Dinić, J.; Banković, J.; Novaković, I.; Šegan, D.; Sladić, D. Simple avarone mimetics as selective agents against multidrug resistant cancer cells. *Eur. J. Med. Chem.,* **2016**, *118*, 107-120. [http://dx.doi.org/10.1016/j.ejmech.2016.04.011] [PMID: 27128177]

[6] Doroshow, J.H. Overcoming resistance to targeted anticancer drugs. *N. Engl. J. Med.,* **2013**, *369*(19), 1852-1853. [http://dx.doi.org/10.1056/NEJMe1311325] [PMID: 24180495]

[7] Jagetia, G.C.; Baliga, M.S.; Venkatesh, P. Effect of Sapthaparna (*Alstonia scholaris Linn*) in modulating the benzo(a)pyrene-induced forestomach carcinogenesis in mice. *Toxicol. Lett.,* **2003**, *144*(2), 183-193. [http://dx.doi.org/10.1016/S0378-4274(03)00205-4] [PMID: 12927362]

[8] Khattak, S.; Khan, H. Anti-cancer potential of phyto-alkaloids: A prospective review. *Curr. Cancer Ther. Rev.,* **2016**, *12*(1), 66-75. [http://dx.doi.org/10.2174/1573394712666160617081638]

[9] Kantarjian, H.; Stein, A.; Gökbuget, N.; Fielding, A.K.; Schuh, A.C.; Ribera, J-M.; Wei, A.; Dombret, H.; Foà, R.; Bassan, R.; Arslan, Ö.; Sanz, M.A.; Bergeron, J.; Demirkan, F.; Lech-Maranda, E.; Rambaldi, A.; Thomas, X.; Horst, H-A.; Brüggemann, M.; Klapper, W.; Wood, B.L.; Fleishman, A.; Nagorsen, D.; Holland, C.; Zimmerman, Z.; Topp, M.S. Blinatumomab *versus* chemotherapy for advanced acute lymphoblastic leukemia. *N. Engl. J. Med.,* **2017**, *376*(9), 836-847. [http://dx.doi.org/10.1056/NEJMoa1609783] [PMID: 28249141]

[10] Khan, H. Medicinal plants need biological screening: A future treasure as therapeutic agents. *Biol. Med. (Aligarh),* **2014**, *6*e110 [http://dx.doi.org/10.4172/0974-8369.1000e110]

[11] Save, S.A.; Lonkhande, R.S.; Chowdhary, A.S. *Thevetia peruviana*: The good luck tree. *Innov. Pharm. Pharmacother.,* **2015**, *3*(3), 586-606.

[12] Khan, H. Medicinal plants in light of history recognized therapeutic modality. *J. Evid. Based Complementary Altern. Med.,* **2014**, *19*(3), 216-219. [http://dx.doi.org/10.1177/2156587214533346] [PMID: 24789912]

[13] Aboul-enein, A.M. Adu el-ela, F.; Shalaby, E.; El-shemy, H. Potent anticancer and antioxidant activities of active ingredients separated from Solanum nigrum and Cassia italica Extracts. *J. Afrid Land Studies,* **2014**, *24*(1), 145-152.

[14] Bohé, L.; Crich, D. *6.01 Synthesis of Glycosides A2 - Knochel, Paul,* 2nd ed; Comprehensive Organic Synthesis II, **2014**, pp. 1-33.

[15] Khattak, S.; Khan, H. Phyto-glycosides as therapeutic target in the treatment of diabetes. *Mini Rev. Med. Chem.,* **2018**, *18*(3), 208-215. [http://dx.doi.org/10.2174/1389557516666160909112751] [PMID: 27629995]

[16] Lindhorst, T.K. *Essentials of Carbohydrate Chemistry and Biochemistry,* 3rd ed; Wiley-VCH Weinheim, **2007**.

[17] Zahid, N.I.; Conn, C.E.; Brooks, N.J.; Ahmad, N.; Seddon, J.M.; Hashim, R. Investigation of the effect of sugar stereochemistry on biologically relevant lyotropic phases from branched-chain synthetic glycolipids by small-angle X-ray scattering. *Langmuir,* **2013**, *29*(51), 15794-15804. [http://dx.doi.org/10.1021/la4040134] [PMID: 24274824]

[18] Rathore, H.; From, A.H.; Ahmed, K.; Fullerton, D.S. Cardiac glycosides. 7. Sugar stereochemistry and cardiac glycoside activity. *J. Med. Chem.,* **1986**, *29*(10), 1945-1952. [http://dx.doi.org/10.1021/jm00160a025] [PMID: 3020248]

[19] Schneider, N.F.Z.; Cerella, C.; Simões, C.M.O.; Diederich, M. Anticancer and immunogenic properties of cardiac glycosides. *Molecules,* **2017**, *22*(11), 1932. [http://dx.doi.org/10.3390/molecules22111932] [PMID: 29117117]

[20] Langenhan, J.M.; Peters, N.R.; Guzei, I.A.; Hoffmann, F.M.; Thorson, J.S. Enhancing the anticancer properties of cardiac glycosides by neoglycorandomization. *Proc. Natl. Acad. Sci. USA,* **2005**, *102*(35), 12305-12310. [http://dx.doi.org/10.1073/pnas.0503270102] [PMID: 16105948]

[21] Park, E-H.; Kim, Y-J.; Yamabe, N.; Park, S-H.; Kim, H-K.; Jang, H-J.; Kim, J.H.; Cheon, G.J.; Ham, J.; Kang, K.S. Stereospecific anticancer effects of ginsenoside Rg3 epimers isolated from heat-processed American ginseng on human gastric cancer cell. *J. Ginseng Res.,* **2014**, *38*(1), 22-27. [http://dx.doi.org/10.1016/j.jgr.2013.11.007] [PMID: 24558306]

[22] Jeong, S.M.; Lee, J-H.; Kim, J-H.; Lee, B-H.; Yoon, I-S.; Lee, J-H.; Kim, D-H.; Rhim, H.; Kim, Y.; Nah, S-Y. Stereospecificity of ginsenoside Rg3 action on ion channels. *Mol. Cells,* **2004**, *18*(3), 383-389. [PMID: 15650337]

[23] Bustos-Brito, C.; Sánchez-Castellanos, M.; Esquivel, B.; Calderón, J.S.; Calzada, F.; Yépez-Mulia, L.; Joseph-Nathan, P.; Cuevas, G.; Quijano, L. ent-Kaurene Glycosides from *Ageratina cylindrica*. *J. Nat. Prod.,* **2015**, *78*(11), 2580-2587. [http://dx.doi.org/10.1021/acs.jnatprod.5b00488] [PMID: 26517282]

[24] Okoye, F.B.C.; Sawadogo, W.R.; Sendker, J.; Aly, A.H.; Quandt, B.; Wray, V.; Hensel, A.; Esimone, C.O.; Debbab,

A.; Diederich, M.; Proksch, P. Flavonoid glycosides from *Olax mannii*: Structure elucidation and effect on the nuclear factor kappa B pathway. *J. Ethnopharmacol.,* **2015**, *176*, 27-34. [http://dx.doi.org/10.1016/j.jep.2015.10.019] [PMID: 26475120]

[25] Kereru, P.G.; Keriko, J.M.; Gachanja, A.N.; Keni, G.M. Direct detection of triterpinoids saponin in medicinal plant. *Afr. J. Trad. Compliment. Altern. Med.,* **2008**, *5*(1), 56-60.

[26] Pan, L-L.; Fang, P-L.; Zhang, X-J.; Ni, W.; Li, L.; Yang, L-M.; Chen, C-X.; Zheng, Y-T.; Li, C-T.; Hao, X-J.; Liu, H-Y. Tigliane-type diterpenoid glycosides from *Euphorbia fischeriana*. *J. Nat. Prod.,* **2011**, *74*(6), 1508-1512. [http://dx.doi.org/10.1021/np200058c] [PMID: 21534540]

[27] Mshvildadze, V.; Legault, J.; Lavoie, S.; Gauthier, C.; Pichette, A. Anticancer diarylheptanoid glycosides from the inner bark of *Betula papyrifera*. *Phytochemistry,* **2007**, *68*(20), 2531-2536. [http://dx.doi.org/10.1016/j.phytochem.2007.05.018] [PMID: 17599372]

[28] Gan, Y.J.; Mei, W.L.; Zhao, Y.X.; Dai, H.F. A new cytotoxic cardenolide from the latex of *Antiaris toxicaria*. *Chin. Chem. Lett.,* **2009**, *20*(4), 450-452. [http://dx.doi.org/10.1016/j.cclet.2008.12.043]

[29] Sun, L.; Zhao, Y.; Yuan, H.; Li, X.; Cheng, A.; Lou, H. Solamargine, a steroidal alkaloid glycoside, induces oncosis in human K562 leukemia and squamous cell carcinoma KB cells. *Cancer Chemother. Pharmacol.,* **2011**, *67*(4), 813-821. [http://dx.doi.org/10.1007/s00280-010-1387-9] [PMID: 20563579]

[30] Liu, Q.; Tang, J-S.; Hu, M-J.; Liu, J.; Chen, H-F.; Gao, H.; Wang, G-H.; Li, S-L.; Hao, X-J.; Zhang, X-K.; Yao, X.S. Antiproliferative cardiac glycosides from the latex of *Antiaris toxicaria*. *J. Nat. Prod.,* **2013**, *76*(9), 1771-1780. [http://dx.doi.org/10.1021/np4005147] [PMID: 24033101]

[31] Podolak, I.; Galanty, A.; Sobolewska, D. Saponins as cytotoxic agents: A review. *Phytochem. Rev.,* **2010**, *9*(3), 425-474. [http://dx.doi.org/10.1007/s11101-010-9183-z] [PMID: 20835386]

[32] Sun, J.; Lou, H.; Dai, S.; Xu, H.; Zhao, F.; Liu, K. Indole alkoloids from *Nauclea officinalis* with weak antimalarial activity. *Phytochemistry,* **2008**, *69*(6), 1405-1410. [http://dx.doi.org/10.1016/j.phytochem.2008.01.008] [PMID: 18328515]

[33] El-Seedi, H.R.; Burman, R.; Mansour, A.; Turki, Z.; Boulos, L.; Gullbo, J.; Göransson, U. The traditional medical uses and cytotoxic activities of sixty-one Egyptian plants: discovery of an active cardiac glycoside from *Urginea maritima*. *J. Ethnopharmacol.,* **2013**, *145*(3), 746-757. [http://dx.doi.org/10.1016/j.jep.2012.12.007] [PMID: 23228916]

[34] Xue, R.; Han, N.; Ye, C.; Wang, L.; Yang, J.; Wang, Y.; Yin, J. The cytotoxic activities of cardiac glycosides from *Streptocaulon juventas* and the structure-activity relationships. *Fitoterapia,* **2014**, *98*, 228-233. [http://dx.doi.org/10.1016/j.fitote.2014.08.008] [PMID: 25128424]

[35] Zhang, J.; Kurita, M.; Shinozaki, T.; Ukiya, M.; Yasukawa, K.; Shimizu, N.; Tokuda, H.; Masters, E.T.; Akihisa, M.; Akihisa, T. Triterpene glycosides and other polar constituents of shea (*Vitellaria paradoxa*) kernels and their bioactivities. *Phytochemistry,* **2014**, *108*, 157-170. [http://dx.doi.org/10.1016/j.phytochem.2014.09.017] [PMID: 25446237]

[36] Zhong, R.; Guo, Q.; Zhou, G.; Fu, H.; Wan, K. Three new labdane-type diterpene glycosides from fruits of *Rubus chingii* and their cytotoxic activities against five humor cell lines. *Fitoterapia,* **2015**, *102*, 23-26. [http://dx.doi.org/10.1016/j.fitote.2015.01.007] [PMID: 25598186]

[37] Li, Y-W.; Qi, J.; Zhang, Y-Y.; Huang, Z.; Kou, J-P.; Zhou, S-P.; Zhang, Y.; Yu, B-Y. Novel cytotoxic steroidal glycosides from the roots of *Liriope muscari*. *Chin. J. Nat. Med.,* **2015**, *13*(6), 461-466. [http://dx.doi.org/10.1016/S1875-5364(15)30040-6] [PMID: 26073343]

[38] Raees, M.A.; Hussain, H.; Rehman, N.U.; Khan, H.Y.; Abbas, G.; Al-Rawahi, A.; Elyassi, A.; Al-Amri, I.S.; Green, I.R.; Al-Broumi, M.A.; Mahmood, T.; Al-Harrasi, A. Desmiflavasides A and B: Two new bioactive pregnane glycosides from the sap of *Desmidorchis flava*. *Phytochem. Lett.,* **2015**, *12*, 153-157. [http://dx.doi.org/10.1016/j.phytol.2015.03.013]

[39] Fan, B-Y.; Li, Z-R.; Ma, T.; Gu, Y-C.; Zhao, H-J.; Luo, J-G.; Kong, L-Y. Further screening of the resin glycosides in the edible water spinach and characterisation on their mechanism of anticancer potential. *J. Funct. Foods,* **2015**, *19*, 141-154. [http://dx.doi.org/10.1016/j.jff.2015.09.027]

[40] Jia, S.; Liu, X.; Dai, R.; Meng, W.; Chen, Y.; Deng, Y.; Lv, F. Six new polyhydroxy steroidal glycosides from *Dregea sinensis Hemsl*. *Phytochem. Lett.,* **2015**, *11*, 209-214. [http://dx.doi.org/10.1016/j.phytol.2014.12.016]

[41] Xue, R.; Han, N.; Xia, M.; Ye, C.; Hao, Z.; Wang, L.; Wang, Y.; Yang, J.; Saiki, I.; Yin, J. TXA9, a cardiac glycoside from Streptocaulon juventas, exerts a potent anti-tumor activity against human non-small cell lung cancer cells *in vitro* and *in vivo*. *Steroids,* **2015**, *94*, 51-59. [http://dx.doi.org/10.1016/j.steroids.2014.12.015] [PMID: 25555472]

[42] Rascón-Valenzuela, L.; Velázquez, C.; Garibay-Escobar, A.; Medina-Juárez, L.A.; Vilegas, W.; Robles-Zepeda, R.E. Antiproliferative activity of cardenolide glycosides from *Asclepias subulata*. *J. Ethnopharmacol.,* **2015**, *171*, 280-286. [http://dx.doi.org/10.1016/j.jep.2015.05.057] [PMID: 26068432]

[43] Park, S.; Nhiem, N.X.; Lee, T.H.; Kim, N.; Kim, S.Y.; Chae, H-J.; Kim, S.H. Isolation of two new bioactive sesquiterpene lactone glycosides from the roots of *Ixeris dentata*. *Bioorg. Med. Chem. Lett.,* **2015**, *25*(20), 4562-4566. [http://dx.doi.org/10.1016/j.bmcl.2015.08.061] [PMID: 26341134]

[44] Zheng, J-Y.; Wang, Q.; L Iu, Z.X.; Liu, C.X.; Guo, Z.Y.; Zhang, H.Q.; He, H.B.; Tu, X.; Zou, K. Two new steroidal glycosides with unique structural feature of 14α-hydroxy-5β-steroids from *Reineckia carnea*. *Fitoterapia,* **2016**, *115*, 19-23. [http://dx.doi.org/10.1016/j.fitote.2016.09.014] [PMID: 27693739]

[45] Xue, Z.; Yan, R.; Yang, B. Phenylethanoid glycosides and phenolic glycosides from stem bark of *Magnolia officinalis*. *Phytochemistry,* **2016**, *127*, 50-62. [http://dx.doi.org/10.1016/j.phytochem.2016.03.011] [PMID: 27086163]

[46] Raees, M.A.; Hussain, H.; Al-Rawahi, A.; Csuk, R.; Muhammad, S.A.; Khan, H.Y.; Rehman, N.U.; Abbas, G.; Al-Broumi, M.A.; Green, I.R.; Elyassi, A.; Mahmood, T.; Al-Harrasi, A. Anti-proliferative and computational studies of two new pregnane glycosides from *Desmidorchis flava*. *Bioorg. Chem.,* **2016**, *67*, 95-104. [http://dx.doi.org/10.1016/j.bioorg.2016.05.008] [PMID: 27299811]

[47] Shah, Z.A.; Hameed, A.; Ahmed, A.; Simjee, S.U.; Jabeen, A.; Ullah, A.; Shaheen, F. Cytotoxic and anti-inflammatory salicin glycosides from leaves of *Salix acmophylla*. *Phytochem. Lett.,* **2016**, *17*, 107-113. [http://dx.doi.org/10.1016/j.phytol.2016.07.013]

[48] Verma, A.; Ahmed, B.; Anwar, F.; Rahman, M.; Patel, D.K.; Kaithwas, G.; Rani, R.; Bhatt, P.C.; Kumar, V. Novel glycoside from *Wedelia calendulacea* inhibits diethyl nitrosamine-induced renal cancer *via* downregulating the COX-2 and PEG_2 through nuclear factor-κB pathway. *Inflammopharmacology,* **2017**, *25*(1), 159-175. [http://dx.doi.org/10.1007/s10787-017-0310-y] [PMID: 28155120]

[49] Shahzad, N.; Khan, W.; Md, S.; Ali, A.; Saluja, S.S.; Sharma, S.; Al-Allaf, F.A.; Abduljaleel, Z.; Ibrahim, I.A.A.; Abdel-Wahab, A.F.; Afify, M.A.; Al-Ghamdi, S.S. Phytosterols as a natural anticancer agent: Current status and future perspective. *Biomed. Pharmacother.,* **2017**, *88*, 786-794. [http://dx.doi.org/10.1016/j.biopha.2017.01.068] [PMID: 28157655]

[50] Guo, L.; Lv, G.; Qiu, L.; Yang, H.; Zhang, L.; Yu, H.; Zou, M.; Lin, J. Insights into anticancer activity and mechanism of action of a ruthenium(II) complex in human esophageal squamous carcinoma EC109 cells. *Eur. J. Pharmacol.,* **2016**, *786*, 60-71. [http://dx.doi.org/10.1016/j.ejphar.2016.05.042] [PMID: 27262377]

[51] Lei, Y.; Zhang, D.; Yu, J.; Dong, H.; Zhang, J.; Yang, S. Targeting autophagy in cancer stem cells as an anticancer therapy. *Cancer Lett.,* **2017**, *393*, 33-39. [http://dx.doi.org/10.1016/j.canlet.2017.02.012] [PMID: 28216370]

[52] Cerella, C.; Dicato, M.; Diederich, M. Assembling the puzzle of anti-cancer mechanisms triggered by cardiac glycosides. *Mitochondrion,* **2013**, *13*(3), 225-234. [http://dx.doi.org/10.1016/j.mito.2012.06.003] [PMID: 22735572]

[53] Cham, B.E. Drug therapy: Solamargine and other solasodine rhamnosyl glycosides as anticancer agents. *Modern Chemother.,* **2013**, *2*(2), 33-49. [http://dx.doi.org/10.4236/mc.2013.22005]

[54] Allan, G.; Ouadid-Ahidouch, H.; Sanchez-Fernandez, E.M.; Risquez-Cuadro, R.; Fernandez, J.M.G.; Ortiz-Mellet, C.; Ahidouch, A. New castanospermine glycoside analogues inhibit breast cancer cell proliferation and induce apoptosis without affecting normal cells. *PLoS One,* **2013**, *8*(10)e76411. [http://dx.doi.org/10.1371/journal.pone.0076411] [PMID: 24124558]

[55] Patel, S. Plant-derived cardiac glycosides: Role in heart ailments and cancer management. *Biomed. Pharmacother.,* **2016**, *84*, 1036-1041. [http://dx.doi.org/10.1016/j.biopha.2016.10.030] [PMID: 27780131]

[56] Song, Z.; Xu, X. Advanced research on anti-tumor effects of amygdalin. *J. Cancer Res. Ther.,* **2014**, *10*(Suppl. 1), 3-7. [http://dx.doi.org/10.4103/0973-1482.139743] [PMID: 25207888]

[57] Leu, W-J.; Chang, H-S.; Chan, S-H.; Hsu, J-L.; Yu, C-C.; Hsu, L-C.; Chen, I.S.; Guh, J-H.; Reevesioside, A. Reevesioside A, a cardenolide glycoside, induces anticancer activity against human hormone-refractory prostate cancers through suppression of c-myc expression and induction of G1 arrest of the cell cycle. *PLoS One,* **2014**, *9*(1)e87323 [http://dx.doi.org/10.1371/journal.pone.0087323] [PMID: 24475272]

[58] Rascón Valenzuela, L.A.; Jiménez Estrada, M.; Velázquez Contreras, C.A.; Garibay Escobar, A.; Medina Juárez, L.A.; Gámez Meza, N.; Robles Zepeda, R.E. Antiproliferative and apoptotic activities of extracts of *Asclepias subulata*. *Pharm. Biol.,* **2015**, *53*(12), 1741-1751. [http://dx.doi.org/10.3109/13880209.2015.1005752] [PMID: 25853961]

[59] Rascón-Valenzuela, L.A.; Velázquez, C.; Garibay-Escobar, A.; Vilegas, W.; Medina-Juárez, L.A.; Gámez-Meza, N.; Robles-Zepeda, R.E. Apoptotic activities of cardenolide glycosides from *Asclepias subulata*. *J. Ethnopharmacol.,* **2016**, *193*, 303-311. [http://dx.doi.org/10.1016/j.jep.2016.08.022] [PMID: 27545974]

[60] Fan, B-Y.; Li, Z-R.; Ma, T.; Gu, Y-C.; Zhao, H-J.; Luo, J-G.; Kong, L-Y. Further screening of the resin glycosides in the edible water spinach and characterisation on their mechanism of anticancer potential. *J. Funct. Foods,* **2015**, *19*, 141-154. [http://dx.doi.org/10.1016/j.jff.2015.09.027]

[61] Aminin, D.L.; Menchinskaya, E.S.; Pisliagin, E.A.; Silchenko, A.S.; Avilov, S.A.; Kalinin, V.I. Anticancer activity of sea cucumber triterpene glycosides. *Mar. Drugs,* **2015**, *13*(3), 1202-1223. [http://dx.doi.org/10.3390/md13031202] [PMID: 25756523]

[62] Okoye, F.B.; Sawadogo, W.R.; Sendker, J.; Aly, A.H.; Quandt, B.; Wray, V.; Hensel, A.; Esimone, C.O.; Debbab, A.; Diederich, M.; Proksch, P. Flavonoid glycosides from *Olax mannii*: Structure elucidation and effect on the nuclear factor kappa B pathway. *J. Ethnopharmacol.,* **2015**, *176*, 27-34. [http://dx.doi.org/10.1016/j.jep.2015.10.019] [PMID: 26475120]

[63] Polkowski, K.; Popiołkiewicz, J.; Krzeczyński, P.; Ramza, J.; Pucko, W.; Zegrocka-Stendel, O.; Boryski, J.; Skierski, J.S.; Mazurek, A.P.; Grynkiewicz, G. Cytostatic and cytotoxic activity of synthetic genistein glycosides against human cancer cell lines. *Cancer Lett.,* **2004**, *203*(1), 59-69. [http://dx.doi.org/10.1016/j.canlet.2003.08.023] [PMID: 14670618]

[64] Lamartiniere, C.A. Protection against breast cancer with genistein: A component of soy. *Am. J. Clin. Nutr.,* **2000**, *71*(6)(Suppl.), 1705S-1707S. [http://dx.doi.org/10.1093/ajcn/71.6.1705S] [PMID: 10837323]

[65] Messina, M.J.; Persky, V.; Setchell, K.D.; Barnes, S. Soy intake and cancer risk: a review of the *in vitro* and *in vivo* data. *Nutr. Cancer,* **1994**, *21*(2), 113-131. [http://dx.doi.org/10.1080/01635589409514310] [PMID: 8058523]

[66] Morabito, N.; Crisafulli, A.; Vergara, C.; Gaudio, A.; Lasco, A.; Frisina, N.; D'Anna, R.; Corrado, F.; Pizzoleo, M.A.; Cincotta, M.; Altavilla, D.; Ientile, R.; Squadrito, F. Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: A randomized double-blind placebo-controlled study. *J. Bone Miner. Res.,* **2002**, *17*(10), 1904-1912. [http://dx.doi.org/10.1359/jbmr.2002.17.10.1904] [PMID: 12369794]

[67] Squadrito, F.; Altavilla, D.; Morabito, N.; Crisafulli, A.; D'Anna, R.; Corrado, F.; Ruggeri, P.; Campo, G.M.; Calapai, G.; Caputi, A.P.; Squadrito, G. The effect of the phytoestrogen genistein on plasma nitric oxide concentrations, endothelin-1 levels and endothelium dependent vasodilation in postmenopausal women. *Atherosclerosis,* **2002**, *163*(2), 339-347.

[http://dx.doi.org/10.1016/S0021-9150(02)00013-8] [PMID: 12052481]

[68] Popiołkiewicz, J.; Polkowski, K.; Skierski, J.S.; Mazurek, A.P. *In vitro* toxicity evaluation in the development of new anticancer drugs-genistein glycosides. *Cancer Lett.,* **2005**, *229*(1), 67-75. [http://dx.doi.org/10.1016/j.canlet.2005.01.014] [PMID: 16157220]

[69] Iyer, A.K.; Zhou, M.; Azad, N.; Elbaz, H.; Wang, L.; Rogalsky, D.K.; Rojanasakul, Y.; O'Doherty, G.A.; Langenhan, J.M. A direct comparison of the anticancer activities of digitoxin MeON-neoglycosides and O-Glycosides: Oligosaccharide chain length-dependent induction of caspase-9-mediated apoptosis. *ACS Med. Chem. Lett.,* **2010**, *1*(7), 326-330. [http://dx.doi.org/10.1021/ml1000933] [PMID: 21103068]

[70] Nandurkar, N.S.; Zhang, J.; Ye, Q.; Ponomareva, L.V.; She, Q.B.; Thorson, J.S. The identification of perillyl alcohol glycosides with improved antiproliferative activity. *J. Med. Chem.,* **2014**, *57*(17), 7478-7484. [http://dx.doi.org/10.1021/jm500870u] [PMID: 25121720]

[71] Bkhaitan, M.M.; Mirza, A.Z.; Shamshad, H.; Ali, H.I. Identification of potent virtual leads and ADME prediction of isoxazolidine podophyllotoxin derivatives as topoisomerase II and tubulin inhibitors. *J. Mol. Graph. Model.,* **2017**, *73*, 74-93. [http://dx.doi.org/10.1016/j.jmgm.2017.01.015] [PMID: 28242581]

[72] Chen, C.; Yu, Y.; Wang, X.; Shi, P.; Wang, Y.; Wang, P. Manipulation of pH-Sensitive interactions between podophyllotoxin-chitosan for enhanced controlled drug release. *Int. J. Biol. Macromol.,* **2017**, *95*, 451-461. [http://dx.doi.org/10.1016/j.ijbiomac.2016.11.053] [PMID: 27867056]

[73] Zhang, L.; Liu, L.; Zheng, C.; Wang, Y.; Nie, X.; Shi, D.; Chen, Y.; Wei, G.; Wang, J. Synthesis and biological evaluation of novel podophyllotoxin-NSAIDs conjugates as multifunctional anti-MDR agents against resistant human hepatocellular carcinoma Bel-7402/5-FU cells. *Eur. J. Med. Chem.,* **2017**, *131*, 81-91. [http://dx.doi.org/10.1016/j.ejmech.2017.03.011] [PMID: 28301815]

[74] Zi, C-T.; Yang, D.; Dong, F-W.; Li, G-T.; Li, Y.; Ding, Z-T.; Zhou, J.; Jiang, Z-H.; Hu, J-M. Synthesis and antitumor activity of novel per-butyrylated glycosides of podophyllotoxin and its derivatives. *Bioorg. Med. Chem.,* **2015**, *23*(7), 1437-1446. [http://dx.doi.org/10.1016/j.bmc.2015.02.021] [PMID: 25744190]

[75] Sun, W-X.; Ji, Y-J.; Wan, Y.; Han, H-W.; Lin, H-Y.; Lu, G-H.; Qi, J-L.; Wang, X-M.; Yang, Y-H. Design and synthesis of piperazine acetate podophyllotoxin ester derivatives targeting tubulin depolymerization as new anticancer agents. *Bioorg. Med. Chem. Lett.,* **2017**, *27*(17), 4066-4074. [http://dx.doi.org/10.1016/j.bmcl.2017.07.047] [PMID: 28757065]

[76] Zhang, X.; Rakesh, K.P.; Shantharam, C.S.; Manukumar, H.M.; Asiri, A.M.; Marwani, H.M.; Qin, H-L. Podophyllotoxin derivatives as an excellent anticancer aspirant for future chemotherapy: A key current imminent needs. *Bioorg. Med. Chem.,* **2018**, *26*(2), 340-355. [http://dx.doi.org/10.1016/j.bmc.2017.11.026] [PMID: 29269253]

[77] Khan, N.; Sharma, S.; Sultana, S. Amelioration of ferric nitrilotriacetate (Fe-NTA) induced renal oxidative stress and tumor promotion response by coumarin (1,2-benzopyrone) in Wistar rats. *Cancer Lett.,* **2004**, *210*(1), 17-26. [http://dx.doi.org/10.1016/j.canlet.2004.01.011] [PMID: 15172116]

[78] Verma, A.; Bhatt, P.C.; Kaithwas, G.; Sethi, N.; Rashid, M.; Singh, Y.; Rahman, M.; Al-Abbasi, F.; Anwar, F.; Kumar, V. Chemomodulatory effect *Melastoma Malabathricum Linn* against chemically induced renal carcinogenesis rats *via* attenuation of inflammation, oxidative stress, and early markers of tumor expansion. *Inflammopharmacology,* **2016**, *24*(5), 233-251. [http://dx.doi.org/10.1007/s10787-016-0276-1] [PMID: 27628241]

[79] Sablina, A.A.; Budanov, A.V.; Ilyinskaya, G.V.; Agapova, L.S.; Kravchenko, J.E.; Chumakov, P.M. The antioxidant function of the p53 tumor suppressor. *Nat. Med.,* **2005**, *11*(12), 1306-1313. [http://dx.doi.org/10.1038/nm1320] [PMID: 16286925]

[80] Maran, J.P.; Priya, B.; Manikandan, S. Modeling and optimization of supercritical fluid extraction of anthocyanin and phenolic compounds from *Syzygium cumini* fruit pulp. *J. Food Sci. Technol.,* **2014**, *51*(9), 1938-1946. [http://dx.doi.org/10.1007/s13197-013-1237-y] [PMID: 25190849]

[81] Teo, C.C.; Tan, S.N.; Yong, J.W.H.; Hew, C.S.; Ong, E.S. Pressurized hot water extraction (PHWE). *J. Chromatogr. A,* **2010**, *1217*(16), 2484-2494. [http://dx.doi.org/10.1016/j.chroma.2009.12.050] [PMID: 20060531]

[82] Plaza, M.; Turner, C. Pressurized hot water extraction of bioactives. *Trends Analyt. Chem.,* **2015**, *71*, 39-54. [http://dx.doi.org/10.1016/j.trac.2015.02.022]

[83] Liau, B-C.; Ponnusamy, V.K.; Lee, M-R.; Jong, T-T.; Chen, J-H. Development of pressurized hot water extraction for five flavonoid glycosides from defatted *Camellia oleifera* seeds (byproducts). *Ind. Crops Prod.,* **2017**, *95*, 296-304. [http://dx.doi.org/10.1016/j.indcrop.2016.10.034]

[84] Muilenburg, V.L.; Phelan, P.L.; Bonello, P.; Herms, D.A. Inter- and intra-specific variation in stem phloem phenolics of paper birch (*Betula papyrifera*) and European white birch (*Betula pendula*). *J. Chem. Ecol.,* **2011**, *37*(11), 1193-1202. [http://dx.doi.org/10.1007/s10886-011-0028-z] [PMID: 22012323]

[85] Sun, X.; Huo, X.; Luo, T.; Li, M.; Yin, Y.; Jiang, Y. The anticancer flavonoid chrysin induces the unfolded protein response in hepatoma cells. *J. Cell. Mol. Med.,* **2011**, *15*(11), 2389-2398. [http://dx.doi.org/10.1111/j.1582-4934.2010.01244.x] [PMID: 21199322]

[86] Lin, C-N.; Lu, C-M.; Cheng, M-K.; Gan, K-H.; Won, S-J. The cytotoxic principles of *Solanum incanum*. *J. Nat. Prod.,* **1990**, *53*(2), 513-516. [http://dx.doi.org/10.1021/np50068a041] [PMID: 2380724]

[87] Shi, L-S.; Liao, Y-R.; Su, M-J.; Lee, A-S.; Kuo, P-C.; Damu, A.G.; Kuo, S-C.; Sun, H-D.; Lee, K-H.; Wu, T-S. Cardiac glycosides from *Antiaris toxicaria* with potent cardiotonic activity. *J. Nat. Prod.,* **2010**, *73*(7), 1214-1222. [http://dx.doi.org/10.1021/np9005212] [PMID: 20553004]

[88] Tuncok, Y.; Kozan, O.; Cavdar, C.; Guven, H.; Fowler, J. *Urginea maritima (squill)* toxicity. *J. Toxicol. Clin. Toxicol.,* **1995**, *33*(1), 83-86. [http://dx.doi.org/10.3109/15563659509020221] [PMID: 7837318]

[89] Ueda, J-Y.; Tezuka, Y.; Banskota, A.H.; Tran, Q.L.; Tran, Q.K.; Saiki, I.; Kadota, S. Constituents of the Vietnamese medicinal plant *Streptocaulon juventas* and their antiproliferative activity against the human HT-1080 fibrosarcoma cell line. *J. Nat. Prod.,* **2003**, *66*(11), 1427-1433. [http://dx.doi.org/10.1021/np030177h] [PMID: 14640513]

[90] Ojo, O.; Nadro, M.; Tella, I. Protection of rats by extracts of some common Nigerian trees against acetaminophen-induced hepatotoxicity. *Afr. J. Biotechnol.,* **2006**, *5*(9), 755-760.

[91] Ohtani, K.; Yang, C-R.; Miyajima, C.; Zhou, J.; Tanaka, O. Labdane-type diterpene glycosides from fruits of *Rubus foliolosus*. *Chem. Pharm. Bull. (Tokyo),* **1991**, *39*(9), 2443-2445. [http://dx.doi.org/10.1248/cpb.39.2443]

[92] Jiang, C.; Liu, Z-H.; Li, L.; Lin, B-B.; Yang, F.; Qin, M-J. A new eudesmane sesquiterpene glycosides from *Liriope muscari*. *J. Asian Nat. Prod. Res.,* **2012**, *14*(5), 491-495. [http://dx.doi.org/10.1080/10286020.2012.668533] [PMID: 22423627]

[93] Hussain, H.; Raees, M.A.; Rehman, N.U.; Al-Rawahi, A.; Csuk, R.; Khan, H.Y.; Abbas, G.; Al-Broumi, M.A.; Green, I.R.; Elyassi, A.; Mahmood, T.; Al-Harrasi, A. Nizwaside: A new anticancer pregnane glycoside from the sap of *Desmidorchis flava*. *Arch. Pharm. Res.,* **2015**, *38*(12), 2137-2142. [http://dx.doi.org/10.1007/s12272-015-0653-0] [PMID: 26335549]

[94] Fan, B-Y.; Gu, Y-C.; He, Y.; Li, Z-R.; Luo, J-G.; Kong, L-Y. Cytotoxic resin glycosides from *Ipomoea aquatica* and their effects on intracellular Ca2+ concentrations. *J. Nat. Prod.,* **2014**, *77*(10), 2264-2272. [http://dx.doi.org/10.1021/np5005246] [PMID: 25314138]

[95] Liu, Y.; Tang, W.; Yu, S.; Qu, J.; Liu, J.; Liu, Y. Eight new C-21 steroidal glycosides from *Dregea sinensis* var. corrugata. *Steroids,* **2007**, *72*(6-7), 514-523. [http://dx.doi.org/10.1016/j.steroids.2007.03.002] [PMID: 17482655]

[96] Xue, R.; Han, N.; Ye, C.; Wang, H-B.; Yin, J. Cardenolide glycosides from root of *Streptocaulon juventas*. *Phytochemistry,* **2013**, *88*, 105-111. [http://dx.doi.org/10.1016/j.phytochem.2012.12.004] [PMID: 23286880]

[97] Fumiko, A.; Mori, Y.; Yamauchi, T. Cardenolide glycosides from the seeds of *Asclepias curassavica*. *Chem. Pharm. Bull. (Tokyo),* **1992**, *40*(11), 2917-2920. [http://dx.doi.org/10.1248/cpb.40.2917]

[98] Song, X.; Zhang, D.; He, H.; Li, Y.; Yang, X.; Deng, C.; Tang, Z.; Cui, J.; Yue, Z. Steroidal glycosides from *Reineckia carnea*. *Fitoterapia,* **2015**, *105*, 240-245. [http://dx.doi.org/10.1016/j.fitote.2015.07.008] [PMID: 26186990]

[99] Nakazawa, T.; Yasuda, T.; Ohsawa, K. Metabolites of orally administered *Magnolia officinalis* extract in rats and man and its antidepressant-like effects in mice. *J. Pharm. Pharmacol.,* **2003**, *55*(11), 1583-1591. [http://dx.doi.org/10.1211/0022357022188] [PMID: 14713371]

[100] Raees, M.A.; Hussain, H.; Rehman, N.U.; Khan, H.Y.; Abbas, G.; Al-Rawahi, A.; Elyassi, A.; Al-Amri, I.S.; Green, I.R.; Al-Broumi, M.A. Desmiflavasides A and B: Two new bioactive pregnane glycosides from the sap of *Desmidorchis flava*. *Phytochem. Lett.,* **2015**, *12*, 153-157. [http://dx.doi.org/10.1016/j.phytol.2015.03.013]

[101] Raees, M.A.; Hussain, H.; Al-Rawahi, A.; Csuk, R.; Muhammad, S.A.; Khan, H.Y.; Rehman, N.U.; Abbas, G.; Al-Broumi, M.A.; Green, I.R.; Elyassi, A.; Mahmood, T.; Al-Harrasi, A. Anti-proliferative and computational studies of two new pregnane glycosides from *Desmidorchis flava*. *Bioorg. Chem.,* **2016**, *67*, 95-104. [http://dx.doi.org/10.1016/j.bioorg.2016.05.008] [PMID: 27299811]

[102] Salem, A-F.Z.; Salem, M.Z.; González-Ronquillo, M.; Camacho, L.; Cipriano, M. Major chemical constituents of *Leucaena leucocephala* and *Salix babylonica* leaf extracts. *J. Trop. Agric.,* **2011**, *49*, 95-98.

[103] Verma, A.; Singh, D.; Anwar, F.; Bhatt, P. C.; Al-Abbasi, F.; Kumar, V. Triterpenoids principle of *Wedelia calendulacea* attenuated diethynitrosamine-induced hepatocellular carcinoma *via* down-regulating oxidative stress, inflammation and pathology *via* NF-kB pathway. *Inflammopharmacology,* **2018**, *26*(1), 133-146.