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REVIEW PAPER

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Anticancer properties of *Viburnum*

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ABSTRACT

Aim. The aim of this paper is to provide an overview of the anticancer properties of different species of *Viburnum*.

Materials and methods. Forty nine papers that discuss the medicinal history and current research of *Viburnum species* as phytotherapeutic agent were used for this discussion.

Literature analysis. The results of scientific research conducted in vitro indicate that the compounds present in the extracts of Viburnum significantly affect the development of cancer cells such as leukemia, cervical cancer, breast, colon, lung, skin and stomach. This indicates that they may be used as a therapeutic agent to support oncological therapies.

Keywords. antitumor activity, *Viburnum species*, cytotoxic activity

Introduction

Viburnum (*Viburnum L.*) is a shrub currently belonging to the family *Adoxaceae* previously *Viburnaceae* or *Caprifoliaceae* and within the genus represents over 250 species around the world.[1] It is a species widely distributed in the temperate zone in central and southern Europe and North America and in the mountains of northern Africa and south-east Asia.[2-4] In Poland, the wild species found are viburnum coral (*Viburnum opulus*) (Figure 1 and 2) and viburnum hordowina (*V. lantana*).[5] It is a shrub blooming white (Figure 3) – marginal and middle pink-white flowers.

Figure 1. Fruit of viburnum coral (*Viburnum opulus)* (photo by Małgorzata Szczygieł)

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

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Figure 2. Shrub of viburnum coral with ripe fruits (photo by Małgorzata Szczygieł)

Figure 3. Shrub of viburnum coral with flowers (photo by Amelia Prus)

Many species of *Viburnum* are widely known and have been used for many years in folk medicine due to its valuable properties. They are also characterized by antibacterial, anti-inflammatory, sedative, hepatoprotective, antinociceptive and anti-asthmatic properties.[6-9] Numerous biologically active compounds are responsible for these properties which originate from various species of *Viburnum*.[10-16] The scientific literature presents the results of phytochemical studies confirming the presence of triterpenoid compounds [17-22], iodoids, [23-25] diterpenoid/diterpenes [26,7], vibroids, lignans [31-34], flavonoids [35-36], polyphenols [18-27], and vitamins in fruit, leaves, twigs of various species of Viburnum (table 1). These compounds are an important group among compounds derived from natural products in the prevention and treatment of tumors. Our review presents the characteristics of cytotoxic and antineoplastic extracts and compounds isolated from various species of *Viburnum*.

Waheed et al. (2013) in their study analyzed the obtained extract and fractions from the leaves of Viburnum foetens L. for interaction with human breast tumor cell lines (MDA-MB-468) and colon (Caco-2).[37] Based on the analysis of the obtained incubation results with these cell lines, they determined that the extract (organic solvents) and selected fractions inhibited cell proliferation.

Further researchers also undertook the analysis of Bibi et al. to assess Viburnum foetens cytotoxicity against breast cancer cell lines (MCF-7).[38] The phytochemical analysis of the crude extract from the leaves of Viburnum foetens showed the presence of anthraquinones, saponins, tannins, flavonoids and coumarins. On the other hand, the methanol fraction of the extract, less expensive than anthraquinones and saponins, was characterized by the highest high anti-cancer activity.

The above results suggested to researchers the need to undertake further more precise phytochemical analyzes of the obtained extracts and fractions from Viburnum in order to isolate and define specific compounds responsible for cytotoxic and anticancer properties.

This was accomplished by Fukuyma et al. by determining that the extract obtained from the species Viburnum luzonicum is a source of iridoid glycosides and aglycones (Table 1, item 1). Analysis of the results of incubation of these compounds obtained from the V. luzonicum extract with the same human epithelial tumor cell line (HeLa S3) allowed for an assessment of their cytotoxicity. It was demonstrated that glycosides **1** and **2** and agglutinates **5-9** showed moderate cytotoxicity against this line, while **3** and **4** showed no cytotoxic activity.

Researchers continued research on the isolation of further compounds from the extract from the dried leaves of Viburnum luzonicum. Spectroscopic methods confirmed the chemical structure of four iridoid aldehydes bearing (E) – or (Z) – p-coumaroyl group (**1**-**4**) (Table 1 item 2). The cytotoxicity test of these compounds also against the same HeLa S3 tumor cell line indicated that compounds **1**-**3** exhibited moderate cytotoxicity.[40]

In his research, Cheng et al. (2011)[41] isolated from an extract of Viburnum chingii leaves, oleanane triterpenoids (**1**-**2**) and vibesan diterpenoid (**3**) together with **7** other compounds (**4**-**10**) (Table 1, item 3). They then examined the cytotoxicity of these compounds to human cell lines myeloid leukemia (HL-60), hepatocellular carcinoma (SMMC-7721), alveolar basal epithelial cells (A-549), breast (SK-BR-3) and epithelioid carcinoma (PANC- 1). The highest cytotoxicity for all cell lines was demonstrated by compound **3** and the lowest compounds **2, 4, 5, 9** and **10** with the exception of compound **4** showing no cytotoxicity to the SMMC-7721 cell line.

Li et al. (2015)determined that the branches and leaves of Viburnum odoratissimum var. odoratissimum contain diterpenoids and six known compounds with confirmed structure (Table 1, item 4).[42] Subsequently, they investigated the cytotoxicity assessment of newly

Table 1. Compounds isolated from various species *Viburnum*

Compounds	Method analysis -techniques	References
1. Viburnum		
I. iridoids glucosides: **1**. luzonoside A , **2**. luzonoside B, **3**. luzonoside C, **4**. luzonoside D, **iridoid aglycons bearing (*E*)- or (*Z*)-*p*-coumaroyl groups**: **5**. luzonoid A, **6**. luzonoid B, **7**. luzonoid C, 8. luzonoid D, **9**. luzonoid E, **10**. luzonoid F, **11**. luzonoid G	Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C); Infrared Spectroscopy (IR); High Resolution Electrospray Ionization Mass Spectrometry (HR-ESI MS).	Fukuyama et al. (2004)[39]
2. Viburnum luzonicum		
II. aldehydes: **1**. luzonials A, **2**. luzonials B, **3**. luzonidials A, **4**. luzonidials B	Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C); Infrared Spectroscopy (IR); High Resolution Electrospray Ionization Mass Spectrometry (HR-ESI MS).	Fukuyama et al. (2005)[40]
3. Viburnum chingii		
III. oleanane triterpenoids: **1**.1α,3β- dihydroxy-11α-methoxy-olean-12-ene, **2**.1α,2β--dihydroxy-olean-9(11),12-diene, **3**. vibsane-type diterpenoid: **IV.** vibsaol B, **5**. 2α,3β-dihydroxy-20(29)-lupene, **6**. 6α-hydroxy-3-on-20(29)-lupen-28-oic acid, **7**.3,6-dion-20(29)- lupen-28-oic acid, **8**. hederagenin acid, **9**. castanopsone, **10**. 3α,6β -dihydroxy-20(29)-lupene	Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C); Infrared Spectroscopy (IR); High Resolution Electrospray Ionization Mass Spectrometry (HR-ESI MS).	Chen et al.(2011)[41]
Viburnum odoratissimum var. odoratissimum		
IV. diterpenoids: **1**. dehydrovibsanin G, **2**. (+) - 9′-*0*-senecioyllariciresinol, **3.** vibsanin C, **4**. vibsanin H, **5**. (8 Z) -10-epivibsanin C, **6.** (+)-9′-*0*-isovaleryllariciresinol , **7**. 9-aldehynevibsanol, **8**. vibsanol	Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C); Infrared Spectroscopy (IR); High Resolution Electrospray Ionization Mass Spectrometry (HR-ESI MS).	Li et al. (2015)[42]
Viburnum odoratissimum		
V. vibsane-type diterpenoids: **1**. vibsanin A,	Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C); High Resolution Electrospray Ionization Mass Spectrometry (HR-ESI MS).	Yu et al. (2016) [43]
Viburnum odoratissimum		
VI. diterpenoids: **1**.vibsanol C, **2**. vibsanol D, **3**. vibsanol E, **4**. vibsanol F, **5**.Vibsanol G, **6**. vibsanol H, **7**. vibsanin X.	Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C); Infrared (IR); Electron Impact Mass Spectrometry (EIMS); High Resolution Electrospray Ionization Mass Spectrometry (HR-ESI MS).	He et al. (2016) [44]

Viburnum mongolicium		
VII. nor-dammarane triterpenoids: **1**. 3β,12β-dihydroxy-25,26,27-trinordammara-22-en -24,20-olide , **2**. 3β,12β-dihydroxy-24α-methoxy-25,26,27-trinordammara-20,24-epoxy, **3**. 3β-*0*-acetyl-12β-hydroxy-23,24,25,26,27-hexanordammarane-20-one **4**.12β-*0*-acetyl-15α-hydroxy-17β-methoxy-3-oxo-20,21,22-23,24,25,26,27-octanordammanrane, **5**. 12β-*0*-acetyl-15α,17β-dihydroxy-3-oxo-20,21,22-23,24,25,26,27 -octanordammanrane, **6**.12β,15α-dihydroxy-3-oxo-17-en-20,21,22-23,24,25,26,27-octanordammanrane , **7**.12β-hydroxy-3-oxo-24α-methoxy- 25,26,27- trinordammara-20,24-epoxy, **8**. 3β,12β-dihydroxy-23,24,25,26,27-hexanordammarane-20-one		Wang et al. (2013) [45]
Viburnum sambucinum Reinw. ex Blume		
	Mass Spectrometry (MS) Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C).	Nguyen et al. (2017) [46]
Viburnum hainanense Merr. et Chun		
VIII. nordammarane triterpenes: **1**.12β-O-acetyl-17β-hydoxy-3,15-dioxo-20,21,22,23,24,25,26,27-octanordammanran, **2**.12β-hydoxy-17β-methoxy-3,15-dioxo-20,21,22,23,24,25,26,27-octanordammanran, **3**. 3-12β-Oacetyl-3,15-dioxo-17-en-20,21,22,23,24,25,26,27-octanordammanran, **4**.12β-hydoxy-15α-O-acetyl-3-oxo-17-en-20,21,22,23,24,25,26,27-octanordammanran, **5**. 3β-hydoxy-17-oxo-12-en-20,21,22,23,24,25,26,27-octanordammanran	Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C); Infrared (IR); Ultra Violet (UV); Electron Impact Mass Spectrometry (EIMS); High Resolution Electrospray Ionization Mass Spectrometry (HR-ESI MS).	Wang et al. 2016 [47]
Viburnum awabuki		
X. vibsane-type diterpenoids:, **1**.vibsanin P, **2**.vibsanin Q, **3**. vibsanin R -W **4**. vibsanin S, **5**.vibsanin T, **6**. vibsanin U, **7**. vibsanin V, **8**. vibsanin W	Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C); High Resolution Electrospray Ionization Mass Spectrometry (HR-ESI MS).	El-Gamal et al. (2004) [48]

discovered diterpenes against human tumor cell lines: myeloid leukemia (HL-60), skin (A-431), colon (HT-29), breast (T47-D) and lung (A-549). Both new diterpenoids (**1**, **2** compounds) showed inhibitory activity against the human tumor cell lines A431 and T47D. Compound 1 showed higher inhibitory activity on these two cell lines than compound 2.

In the work of Yu et al. (2016) a study of vibsanin A, a vibrate diterpenoid isolated from leaves and twigs Viburnum odoratissimum against the human myeloid leukemia cell line (HL-60) was performed (Table 1, item 5).[43] It was determined that vibsan A induces the differentiation of myeloid leukemia cells. These results indicate that vibsanine A is a powerful tool to understand the potential pathophysiological and therapeutic roles of PKC and justifies further assessment as a potential therapy for differentiating myeloid leukemia.

In subsequent studies, also the analysis of the extract of leaves and twigs Viburnum odoratissimum confirmed the new vibansan diterpenes, vibsanol C-H (**1**-**6**) and vibsanin X (**7**) (Table 1, item 6).[44] Their cytotoxicity was evaluated against human tumor cell lines. Based on the results of the tests, it was found that compound **1** showed significant cytotoxicity to all human cell lines tested: myeloid leukemia (HL-60), cancer liver (SMMC-7721), cancer lung (A-549), breast cancer (MCF-7) and cancer colon (SW-480). Compounds **4** and **5** showed only significant cytotoxicity against the SMMC-7721 cell line, while compounds **3**, **6** and **7** are not cytotoxic.

Successive researchers (Wang et al., 2013) determined that another species Viburnum mongolicium is a source of triterpenoid (Table 1. item 7).[45] Isolated compounds were incubated with 7 human tumor cell lines: lung (A-549), gastric carcinoma (BGC-823), hepatocellular carcinoma (HepG2), myeloid leukemia (HL-60), breast (MCF-7), hepatocellular carcinoma liver (SMMC-7721) and colon (W-480)) to assess their potential for cytotoxicity and antioxidant properties (free radical scavenging activity). Compounds **4**-**6** showed the highest cytotoxic activity against all tumor cell lines tested and antioxidant properties. However, compounds **2** and **7** showed lower values, while compounds **3** and **8** showed the lowest cytotoxic potential. Compound **1** was determined to have no cytotoxic activity.

Nygem et al. showed that leaf extracts from V. sambucinum Reinw. ex Blume contains, among others, dammarane type triterpenoid and other compounds (Table 1. item 8).[46] Analysis of the interaction of the isolated compounds from the extract of this kind of Viburnum relative to the following human cell lines were tested: epithelial carcinoma in the mouth (KB), hepatocellular carcinoma (HepG-2), cancer lung (LU-1) and breast cancer (MCF-7). The dominating activity revealed derivatives of octaordamarane compounds **6** and **7** in all analyzed 4 cell lines. In contrast, compound **1** was more active against LU-1, HepG2 and MCF7 cell lines than KB cell lines, and ursolic acid (**10**) only with LU-1 and MCF-7 cell lines. The compounds **5,9,13,15,16** were characterized by cytotoxic activity and the remaining compounds by non-cytotoxicity.

On the other hand, it was determined by the spectral methods that the extract from the entire plant Viburnum Hainanense Merr. et Chun are nor-dammaran triterpenes (Table 1. Item 9).[47] Isolated compounds were tested for their cytotoxic properties to human tumor cells: cervix carcinoma (Hep-2), skin squamous cell carcinoma (SCL-1), squamous cell carcinoma (CAL-27), head and neck squamous carcinoma (UMSCC-1), pharyngeal carcinoma (Detroit 562) and squamous carcinoma (TCA-83). It was determined that compounds **1**-**4** showed cytotoxicity against all tested cancer cell lines resulting, inter alia, in from the presence of the corresponding tri-terpenes of an acetylene group or a hydroxyl group in the C-12, α, β-unsaturated ketonic at C-15 position.

A vibsane -typ diterpenoids / vibsane diterpenoids (**1**-**8**) were identified in the extract fractions of leaves and twigs Viburnum avabuki K. Koch. (Table 1, item 10).[48] Their cytotoxicity was tested against the cell lines: A549 (human lung adenocarcinoma), HT-29 (human colon adenocarcinoma), and P-388 (mouse lymphocytic leukemia). They showed significant cytotoxic properties against the P-388 mouse cell line compounds **1** and **8**, and lower cytotoxicity of compounds **2**-**7** against the same cell line. However, in comparison to other human tumor cell lines, compounds **1**-**8** were characterized by moderate cytotoxic properties.

Conclusion

Plants of the genus Viburnum are very popular among medicinal plants. They are a rich source of compounds with biological activity, especially anti-proliferative, against numerous human tumor cell lines, which is confirmed by the results of scientific research presented in our article. This suggests that isolated compounds from Viburnum may be an important element in the prevention and treatment of cancer, of course after a positive assessment of their interaction with the recommended drugs. It is necessary to conduct further research on the identification of further active components of Viburnum extracts to assess their cytotoxic activity and anti-cancer properties, as well as to explain the course of changes at the cellular level.

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