Lignans: a versatile source of anticancer drugs

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Abstract

Background: Cancer is considered as the second deadliest disease globally. Plants have continuously offered unique secondary metabolites with remarkable biological applications. Lignans have gained great importance due to their biological activity. Previous studies revealed that the most remarkable bioactivity of lignan class of molecules is anticancer. They are derived from the oxidative dimerization of two phenylpropanoid units. This review covers the isolated anticancer lignans and their mechanistic aspects.

Main body: A bibliographic investigation was performed by analyzing the information available on anticancer lignans in the internationally accepted scientific databases including Web of Science, SciFinder, PubMed, Scopus, and Google Scholar. In this review we have tried to sum up the isolated anticancerous lignan, its source, active plant part, extract and various cell lines used to establish different studies. Here we have included a total number of 113 natural lignans. Many studies that mainly performed in human cell lines have reported. Very few plants have been evaluated for their in vivo anticancer activity.

Conclusion: It can be concluded that in near future the lignans may be an effective pharmacon for the treatment of cancer. Fruitful areas of future research may be in modifying natural lignans or synthesizing new lignans with structural diversity and potent pharmacological activities. Extensive studies are needed to be done highlighting the mechanism of anticancer action of explored and unexplored plants. The data will definitely attract many researchers to start further experimentation that might lead to the drugs for the cancer treatment.

Keywords: Lignan, Anticancer plants, Podophyllotoxin, Cytotoxicity
1 Background
There is a great burden of disease internationally and cancer is in the top priority due to its high incidence rate that causes disability and premature mortality among human populations [1].

Cancer is not a single disease but it is a group of 100 different and distinguishing disorders that affect the entire physiological balances [2]. It is an uncontrolled growth of cells that have damaged DNA expression [3]. If the spread of these abnormal cells is not managed with certain means, it can lead to worse situations or may be death. These abnormal cells are termed as cancer cells, malignant cells, or tumor cells. Many cancers that comprises of abnormal cells are further recognized by the name of the organ that the abnormal cells originated from (for example, breast cancer, lung cancer, prostate cancer, and colorectal cancer). There are various kinds of cancers depends upon the type of genes associated with specific cancer like sarcomas, carcinomas, leukemia, and lymphomas. Carcinogenesis is a multi-leveled process consists of three noticeable stages, i.e., initiation, promotion, and progression [4]. It is the prime result of disturbances that occurred in two types of genes, tumor suppressor genes (TSG) and oncogenes.

Deaths from cancer are rising continuously worldwide with an estimated 11.5 million deaths in 2030 [5]. The International Agency for Research on Cancer (IARC) estimated a shocking number of 19.3 million new cases including every possible distribution criteria (Fig. 1a, b) and approx 10 million of reported death worldwide [6].

Globally, non-communicable diseases (NCDs) accounted for 71% of total deaths. In India, NCDs were estimated to account for 63% of all deaths, and cancer was one of the leading causes (9%). The projected number of patients with cancer in India is 1,392,179 for the year 2020, and the common five leading origins are breast, lung, mouth, cervix uteri, and tongue [7]. Persons with any type of existing cancer are prone to get affected with coronavirus (SARS-CoV-2), and it is a deadly combination for individuals [8]. Studies revealed that prostate and breast cancer constitutes major types of cancer found, respectively, in men and women [9]. In children the blood cancer and the cancers related to the brain and lymph nodes are more frequent than other types of cancer [10, 11]. There are certain risk factors that increase the development of cancer in any person such as ageing, tobacco, ionizing radiation, some chemical compounds, some viruses and bacteria, alcohol consumption, family history of cancer, certain hormones, and overweight [12].

The treatment options of cancer involve surgery of tumor, radiotherapy and chemotherapy depends upon the stage and location of tumor [13]. But these treatments are very costly and require highly specialized health professionals [14]. Additionally, these chemotherapeutic
Fig. 1  
(a) Global cancer cases distribution types including all age groups of females. Source: GLOBOCAN, 2020.  
(b) Global cancer cases distribution types including all age groups of males. Source: GLOBOCAN, 2020.
agents are not free from side effects like myelosuppres-
sion, mucositis, alopecia, cardiotoxicity, neurotoxicity,
immunosuppression, etc. An ideal anticancer drug would
specifically be cytotoxic toward the cancer cells only and
research findings suggests that phytochemicals and their
derivatives are emerging alternatives for better and less
toxic chemotherapeutic agents [13].

Various active compounds such as podophyllotoxin,
vincristine, vinblastine, taxol, etc., have been isolated
from plants, and these molecules acted as lead metabo-
lites to modify and yield analogues better than the parent
compound for activity with low toxicity and improved
bioavailability [15–17].

There are diverse classes of secondary metabolites
which are biosynthesized by plants and, among them, lig-
nans are identified as the major group of natural products
with a broad range of important bioactivities.

2 Main text
Lignans are the class of plant secondary metabolites
derived from the phenylpropanoid pathway and was first
introduced by Haworth [18]. They play an important role
in plant protection and are also proved to be fruitful in
human nutrition and medicine [19]. The chief sources of
dietary lignans are various vegetables and fruits, legumes,
whole grain cereals, and oilseeds [20, 21]. Sesame and
flax seeds are the edible plant components which are the
most concentrated sources of lignans [22].

2.1 Chemistry of lignans
It is well-established that the supergroup of natural phe-
nolics is biosynthesized through the shikimic acid path-
way. The biodiversity of this lignan class of molecules is
found in various parts of more than 60 families of plants
and they are potential bioactive principles toward can-
cerous cells. Beside their cytotoxic property they are also
useful to treat diabetes, oxidation of living cells as antiox-
didants, cardiovascular diseases, microbial infections, and
other major or minor inflammatory responses [23, 24].
As per the earlier findings, the basic structure of lignan
contains the nine carbon (in a C6-C3 fusion) phenylpro-
pane unit (Fig. 2a) from cinnamyl structures [25] which
was redefined by Haworth [18] as dimer of C6-C3 unit
via β-β' bonding (Fig. 2b). Besides this basic hydrocarbon
skeleton they possess numerous additional side groups
either in the form of aliphatic or aromatic origin and
they are classified accordingly. There are eight subtypes
of major lignans (Fig. 3) such as dibenzylbutane (e.g.,
Enterodiol), dibenzylbutyrolactone (e.g., Enterolactone),
dibenzylbutyrocolactol (e.g., Gnetucleistol F), dibenzocy-
clooctadiene (e.g., Gomisins), aryltetralin (e.g., Podoph-
yllotoxins), arylnaphthalene (e.g., Justicidins), furan
(e.g., Belischmins), and furofuran (e.g., Epimagnolin)
derivatives. Except these eight subtypes, they are also
diversified based on the presence or absence of oxygen
[26, 27]. Hybrid lignans are molecules which have other
secondary metabolites like flavonoids (flavolignans), cou-
marins (coumarinolignans), xanthones (xantholignans),
stilbenes (stilbenolignans), etc., and possess lignan like
biological and chemical properties.

The discovery of Podophyllotoxins as gold standard in
leading lignans along with establishing its cytotoxic prop-
erty and topoisomerase-II inhibitory potentials helped
the research community to develop other clinically
important drugs like etoposide, teniposide, clinical can-
didates like Etopophos, NK611, GL331, etc. [28]. Ward
reported a total number of 83 synthetic and transforma-
tional schemes including stereospecific and asymmetric
consideration [29] to obtain them in laboratory.

There is persistent interest in the cancer-protective
effects of lignans, which have been shown to have an
advantageous anti-tumor effect throughout the early phases of carcinogenesis. The present review, summarizes the recent literature which deals with the lignans isolated from plants having anticancer potential with their reported mechanism of action which are listed in Table 1. Lignans has been considered as the promising anticancer agents.

3 Material and methods
The bibliography was crucially analyzed from worldwide established scientific databases like SCOPUS, PubMed, ScienceDirect, Springerlink, Web of Science, Wiley, SciFinder, and Google Scholar. The botanical names of these selected plant species were verified from the plant list. The inclusion criteria for the selection of data are lignans isolated from Medicinal plants with reported anticancer activity. Both the reviews and the research articles on medicinal plants are considered. The search terms were lignans, anticancer plants containing lignans, chemistry of lignans without narrowing or limiting search items.

4 Conclusions
Lignans are secondary metabolites are also phenolic in nature and have diversity in biological activities. Previous studies revealed that the most remarkable bioactivity of lignan class of molecules are antioxidant and anticancer. This review covers a considerable number of naturally obtained lignans that are reported to have anticancer potential. In this review we have tried to sum up the isolated anti-cancerous lignan, its source, active plant part, extract and various cell lines used to establish different studies. Here we have included a total 113 numbers of natural lignans. Many studies that mainly performed in human cell lines have reported inhibition of enzymes that retards tumor growth. Very few plants have been evaluated for their in vivo anticancer activity.

It can be concluded that in near future the lignans may be an effective pharmacon for the treatment of cancer. Fruitful areas of future research may be in modifying natural lignans or synthesizing new lignans with structural diversity and potent pharmacological activities. However, among the vast numbers of existing plants on this planet, only a few species have been
Fig. 4 Chemical structures of anticancer isolated lignans from plants
Fig. 4 continued
studied so far for their anticancer principles. Extensive studies are needed to be done highlighting the mechanism of anticancer action of explored and unexplored plants.

Potent anticancer lignans reported in this review needed to be further explored in clinical trials on different models for their effectiveness, toxicological studies, and also targeting particular genotoxic profile against a wide range of cancer in both *in vitro* and *in vivo*. These compounds are obtained from plants in very minute quantities so this is one of the main challenges to be addressed in the future and their total synthesis in order to allow further bioactivity studies. The data will definitely attract many researchers to start further experimentation that might lead to the drugs for the cancer treatment and to manufacture new herbal drugs which have significant anticancer potential.
| Name                           | Structure ID (Fig. 4) | Source                              | Extract                          | Part          | Cancer cell line used (in vitro) | IC_{50}  | In vivo | Dose     | Comments                                                                 | Reference |
|-------------------------------|----------------------|-------------------------------------|----------------------------------|---------------|---------------------------------|----------|---------|----------|--------------------------------------------------------------------------|-----------|
| 9-OH-Pinoresinol              | 1                    | *Saussurea salicifolia* (L.) DC, Asteraceae | Chloroform fraction of ethanolic extract | Aerial parts | LS178Y                          | –        | –       | 10 μg/mL  | Ethanolic extract of the plant reduced the growth of leukemia mouse lymphoma cells to 23.8%. It looks like lignan 9-OH-pinoresinol is responsible for the activity which is well known from other plant sources | [30]      |
| Anhydrosecoisolariciresinol   | 2                    | *Linum usitatissimum*, Linaceae     | –                                | Seeds         | MCF-7                           | 100 µM   | –       | –        | The isolated lignan causes 30% inhibition of cell growth as compared to control | [31]      |
| 4-O-(2,3,4′-tri-O-methyl-β-D-xylopyranosyl) diphyllin | 3                    | *Phyllanthus taxifolius*, Phyllanthaceae | –                                | Aerial parts | HCT116                          | 0.08±0.03 µM | –       | –        | In vitro studies has been shown to inhibit the growth of a number of cancer cell. It shows strongest antiproliferative effect on HCT116 cells. The compound induces apoptosis in HCT116 cells by activating caspase-3 pathway and antiproliferative effect is due to promotion of microtubule depolymerization | [32]      |
| Name         | Structure ID (Fig. 4) | Source | Extract | Part               | Cancer cell line used (in vitro) | IC_{50} | In vivo | Dose   | Comments                                                                 |
|--------------|-----------------------|--------|---------|--------------------|----------------------------------|---------|---------|--------|--------------------------------------------------------------------------|
| (+)-Hinokinin| 4                     | Wikstroemia lanceolata, Thymelaeaceae | Methanol | Stems and roots    | P-388                            | 1.54 µg/mL (ED_{50}) |         |        | Showed significant cytotoxic activity                                   | [33]           |
| Vitexin      | 5                     | Vitex negundo, Verbenaceae | Ethanol | Seeds              | MCF-7, ZR-75-1, SK-BR-7, MDA-MB-231, MDA-MB-435s, PC-3, LNCaP and COC1 | 100 mg/kg | In vivo studies done using tumor xenograft models like MCF-7, MA782, MDA-MB-435s, and T47D xenografts for breast, PC-3 for prostate, HeLa cells for cervical, and HepG2 for liver xenograft Vitexins (lignan mixture) has cytotoxic effects on MCF-7, ZR-75-1, SK-BR-7, MDA-MB-231, MDA-MB-435s, PC-3, LNCaP, COC1 cancer cells. Vitexin induced antitumor effect and cytotoxic activity is exerted through proapoptotic process, which is mediated by a decreased Bcl-2/Bax ratio and activation of caspases | [34]           |
| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC$_{50}$ | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|---------------------------------|----------|--------|------|----------|-----------|
| 7-Hydroxymatairesinol (HMR) | 6 | Picea abies, Pinaceae | Acetone–water (9:1) | Heartwood | LNCaP human prostate cancer xenografts in athymic nude male mice | | | | There is significant decrease in tumor volume. A control diet supplemented with 0.15% or 0.30% of HMR was administered to mice and the tumor take rate and growth was observed for 9 weeks. The diet supplemented with HMR has been shown to inhibit the growth of LNCaP tumors. Mice treated with HMR had smaller tumor volume, lower tumor take rate, increased proportion of non-growing tumors, and higher tumor cell apoptotic index compared with controls. Cell proliferation index was also decreased in mice receiving the 0.30% HMR diet when compared with mice receiving the control diet. | [35] |
Table 1 (continued)

| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC_{50} | In vivo | Dose | Comments | Reference |
|------|---------------------|--------|---------|------|---------------------------------|--------|---------|------|----------|-----------|
| 6'-Hydroxy justicidin A, 6'-hydroxy justicidin B, justicidin B | 7, 8, 9 | Justicia procumbens, Acanthaceae | Ethanolic | Whole plant | K562 | 20.4, 3.9 and 45.4 μM | | | All the compounds significantly inhibited the growth of K562 cells by decreasing both proliferation and SOD activity and inducing apoptosis in dose-dependent manner. Activation of caspase-3 pathway suggests that these compounds induce apoptosis through caspase intrinsic or extrinsic pathway | [36] |
| Picropolygamain, Burseranin | 10, 11 | Bursera graveolens, Burseraceae | Methanol | Stem | HT1080 | 1.9, 5.5 μg/mL (ED_{50}) | | | Showed significant cytotoxic activity | [37] |
| (-)-Deoxypodophyllotoxin, (-)-yatein | 12, 13, | Hernandia nymphaeifolia, Hernandiaceae | Methanol | Bark | P-388, KB16, A549, HT-29 | <1 μg/mL (ED_{50}) | | Showed significant cytotoxic activity | [38] |
| Hanultarin, 1,4-O-Diferuloylsescolariciresinol | 14, 15 | Trichosanthes kirilowii, Cucurbitaceae | 80% Aqueous methanol | Seeds | A549, SK-Mel-2, B16F1 | 3–13 μg/mL | | Inhibitory effect on the polymerization of the actin cytoskeleton in normal epidermal keratinocyte (HaCaT cells) has been shown by compound Hanultarin as compared to those of the other isolates | [39] |
Table 1 (continued)

| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC_{50} | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|---------------------------------|--------|--------|------|----------|-----------|
| Phyllanthusmin A | 16 | *Phyllanthus oligospermus*, Phyllanthaceae | Chloroform fraction of methanolic extract | Stems and roots | KB and P-388 | 2.24 µg/mL and 0.13 µg/mL | | | | [40] |
| Cleistanthin A, Cleistanthin A methyl ether, Taxodifolioside | 17, 18, 19 | *Phyllanthus taxodifolius*, Euphorbiaceae | Ethanol fraction of methanol extract | Aerial parts | Five cultured mammalian cell lines. P-388, KB, Col-2, MCF-7 and Lu-1 | Compounds showed GI_{50} value in the range 10^{-6}-10^{-9} M | | | | [41] |
| 5-Methoxy-4-epipodophyllotoxin, 5-methoxypodophyllotoxin | 20, 21 | *Libocedrus chevalier*, Cupressaceae | Ethyl acetate | Bark | KB | 45 µM and 11 µM | | | | [42] |
| Propinquanin B | 22 | *Schisandra propinquia* (Wall.), Schisandraceae | Chloroform | Stems | HL-60, Hep-G2, P-Hep-G2, KB, Bel-7402 | 7.15, 9.81, 14.00, 11.70, 18.81 µM | | | | [43] |
| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC50 | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|---------------------------------|------|---------|------|----------|-----------|
| Beilschmin A, Beilschmin B, Beilschmin C | 23, 24, 25 | Beilschmidea tsangii, Lauraceae | Stems | P-388 and HT-29 | 1.2 and 5.0 µg/mL, 2.2 and 5.1 µg/mL, 3.6 and 10.5 µg/mL | 2.2 and 5.1 µg/mL, 3.6 and 10.5 µg/mL | | | Showned significant cytotoxic activity | [44] |
| Magnolignan A 2-O-β-D-glucopyranoside, Streblus lignanol | 26, 27 | Streblus asper, Moraceae | Chloroform fraction of 75% ethanol | Heartwood | Hep-2 and Hep-G2 | 13.3 µM, 46.4 µM and 10.1 µM, 21.7 µM | | | Both lignans showed medium cytotoxic activity | [45] |
| Erlangerin A to D | 2, 29, 30, 31 | Commiphora erlangeriana, Burseraceae | Resin | EAHy926 and HeLa, LS29 and RAW 264.7 | 68 ± 6, 40 ± 5, 90 ± 5 and 44 ± 9 µg/mL (EC50) | 23 ± 1.4, 40 ± 1.4, 68 ± 6 and 28 ± 0.3 (EC50) | 0.16 ± 0.09, 0.55 ± 0.007, 5.6 ± 1.5 (EC50), and 0.97 ± 0.21 µg/mL (EC50) | 0.026 ± 0.007, 0.026 ± 0.009, 3.5 ± 1 µg/mL (EC25), and 0.11 ± 0.017 µg/mL (EC50) | Erlangerins C and D were similar to podophyllotoxin on the basis of their structure and biological activity so may have same mechanism of action. They induced a concentration-dependent cytotoxicity in RAW 264.7 and cytostatic effect in HeLa, EAHy926, and LS29 cells. But Erlangerins A and B suppressed cell viability at relatively higher concentrations when compared with Erlangerin C and D | [46] |
| Name                        | Structure ID (Fig. 4) | Source            | Extract        | Part     | Cancer cell line used (in vitro) | IC50 In vivo | In vivo | Dose          | Comments                                                                 |
|-----------------------------|----------------------|-------------------|----------------|----------|---------------------------------|--------------|---------|----------------|--------------------------------------------------------------------------|
| Machilin A, (-)-Sesamin, Machilin G, (+)-Galbacin | 32, 33, 34, 35 | Machilus thunbergii, Lauraceae | Dichloromethane | Bark | HCT-15, MCF-7 and A549 | 12.4, 12.4 and 7.9 µM | 4.4, 3.4 and 11.0 µM | 1.4, 2.7 and 8.3 µM | 6.2, 7.9 and 7.9 µM | PLCγ1 plays a key role in proliferation and progression of human cancer. These compounds inhibit PLCγ1 and showed strong antiproliferative activity [47] |
| Enterolactone, Enterodiol   | 36, 37               | Mammalian lignans | LNCaP          | 57 mM and 100 mM | 10–100 microM | Growth of prostate cancer cells were suppressed may be by hormonally dependent and independent mechanisms [48] |
| Matairesinol                | 38                   | Carthamus tinctorius, Asteraceae | Seeds | HL-60 | 60 µM | DNA content histogram was analyzed by flow cytometry and it showed rapid increase in subdiploid cells and a concomitant decrease in diploid cells exposed to 100 µM matairesinol. It was concluded that cell death was due to the DNA damage and apoptosis [49] |
| Name                          | Structure ID (Fig. 4) | Source                  | Extract Part          | Cancer cell line used (in vitro) | IC₅₀          | In vivo | Dose        | Comments                                                                 | Reference |
|-------------------------------|-----------------------|-------------------------|------------------------|---------------------------------|--------------|---------|-------------|--------------------------------------------------------------------------|-----------|
| Nordihydroguaiaretic acid     | 39                    | Larrea tridentata DC.   | Resinous exudate       | Bush                            | 1.9±0.5 µg   |         |             | It caused time and dose-dependent loss of mitochondrial membrane potential (MMP), down regulation of the anti-apoptotic protein bclₓ and an increase of the apoptotic index. It also induced a shift of the culture population to the G2/M phase of the cell cycle | [50]      |
| Epiashantin                   | 40                    | Artemisia absinthium L. | -                      | Warmwood                       | 9.8±4.5 µM   |         |             | The compound caused a time and dose-dependent loss of mitochondrial membrane potential (MMP), down regulation of the anti-apoptotic protein bclₓ and an increase of the apoptotic index | [50]      |
| Arctigenin                    | 41                    | Arctium lappa L.        | -                      | Root                            | 16.5±8.5 µM  |         |             | The compound caused a time and dose-dependent loss of mitochondrial membrane potential (MMP), down regulation of the anti-apoptotic protein bclₓ and an increase of the apoptotic index | [50]      |
| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC_{50} | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|---------------------------------|--------|--------|------|----------|-----------|
| 7′-Hydroxy-3′,4′,5,9,9′-pentamethoxy-3,4-methylene dioxylignan | 42 | Phyllanthus urinaria, Phylanthaceae | Ethyl acetate | Whole plant | HEP-2 | 4.46 µM | | | 7′-hydroxy-3′,4′,5,9,9′-pentamethoxy-3,4-methylene dioxylignan was capable of inhibiting telomerase activity and also could inhibit bcl2 and activate caspase 3 and caspase 8 whose significance in the induction of apoptosis is well known. | [51] |
| (+)-7′-Acetylpicropodophyllin, Epypangamin | 43, 44 | Hernandia ovigera L., Hernandiaceae | Ethyl acetate | Twigs | JB6 | 0.15 and 0.4.2 µg/mL | | | Significant inhibition of the transformation of murine epidermal JB6 cells, Inhibitory effects on EBV activation has been shown by all isolated compounds. | [52] [53] |
| Deoxypodophyllotoxin, 6,7-Demethylenedeoxypodophyllotoxin, 1,2,3,4-Dehydrodeoxypodophyllotoxin, Dehydrodopodophyllotoxin, Bursehernin, Podorhizol, Epimagnolin | 12, 45, 46, 47, 48, 49, 50 | Hernandia ovigera L., Hernandiaceae | Seeds | | | | | | Epstein-Barr virus early antigen activation (EBV-EA) induced by 12-O-tetradecanoylphorbol 13-acetate (TPA) in Raji cells, 550 mol ratio/32 pmol TPA, 510 520 470 470 480 590 |
| Name          | Structure ID (Fig. 4) | Source                  | Extract  | Part       | Cancer cell line used (in vitro) | IC<sub>50</sub> | In vivo                  | Dose | Comments                                                                 | Reference |
|--------------|-----------------------|-------------------------|----------|------------|--------------------------------|----------------|--------------------------|------|---------------------------------------------------------------------------|-----------|
| Arctiin, Arctigenin | S1, 41                | *Saussurea medusa*, Composite | Methanol | Aerial parts |                                |                | Two stage skin carcinogenesis model using DMBA (7,12-dimethylbenz[a]anthracene) and TPA (12-O-tetradecanoyl phorbol-13-acetate) | Both lignans arctiin and arctigenin exhibited a significant inhibitory effect on the tumor promotion induced by DMBA and TPA by both topical application and oral administration. When both compounds were administered orally, reduction in papillomas per mouse at 15 weeks of promotion in case of arctigenin was 4.2 ± 0.1 and Arctiin 4.0 ± 0.2, and at 20 weeks of promotion arctigenin was 6.1 ± 0.1 and Arctiin was 6.1 ± 02 | [54]      |
| Elenoside    | S2                    | *Justicia hyssoptofila L.*, Acanthaceae | Ethanol  | Leaves     | CCRFCEM, K-526, MOLT-4, RPMI-8226 | 79–97% growth inhibition | 10<sup>-4</sup> M | Elenoside was cytotoxic to leukemic cell lines (CCRFCEM, K-526, MOLT-4, RPMI-8226) at a concentration of 10<sup>-4</sup> M (79–97% growth inhibition). Elenoside does not show significant activity at concentration less than 10<sup>-4</sup> | [55]      |
| Name                        | Structure ID (Fig. 4) | Source                          | Extract | Part   | Cancer cell line used (in vitro) | IC₅₀ | In vivo | Dose | Comments                                                                                     | Reference |
|-----------------------------|----------------------|---------------------------------|---------|--------|----------------------------------|------|---------|------|----------------------------------------------------------------------------------------------|-----------|
| Secoisolariciresinol diglycoside | 53                  | Linum usitatissimum, Linaceae   | Ethanolic | Seeds | Female Sprague–Dawley rats       | 2.93 mmoles/g | Increased plasma insulin-like growth factor (IGF-I) concentrations are associated with increased breast cancer risk. Secoisolariciresinol diglycoside reduced plasma IGF-I levels. It inhibit Mammary tumor development in rats | [56]      |
| Phillygenol, Phillyroside, Phillygenoldiglycoside | 54, 55, 56 | Lancea tibetica, Mazaceae       | SMMC-7721, HeLa, V79, B16 |      |                                   |      |         |      | Phillygenol has shown strong cytotoxic activity on the tested cell lines whereas Phillyroside and Phillygenoldiglycoside had little effect on the proliferation of the tested cell lines | [57]      |
| Podophyllotoxins             | 45, 46, 47…          | Podophyllum peltatum, Podophyllum emodi, Podophyllum versicolor, Linum Juniperus | small-cell lung cancer (SCLC) dose: > 1 µg/mL (etoposide) |      | Disrupt the organization of the karyokinetic spindle single-strand and double-strand breaks in DNA through their interactions with DNA topoisomerase II induce cell cycle arrest in the G2-phase of the cell cycle | [17]      |
| Name                        | Structure ID (Fig. 4) | Source                          | Extract   | Part             | Cancer cell line used (in vitro) | IC_{50}               | In vivo Dose | Comments                                                                 | Reference |
|-----------------------------|-----------------------|---------------------------------|-----------|------------------|----------------------------------|------------------------|--------------|--------------------------------------------------------------------------|-----------|
| Ariensin Burseran           | 57, 11, 58            | Bursera microphylla A. Gray, Burseraceae | Methanol  | Resin obtained from the bark of the plant | RAW264.7, M12.C3.F6 murine cancer cell line (macrophages transformed by virus Avelson leukemia) | 9.8, 0.4, 0.2 μM for all three isolated compounds in RAW264.7 and 2.5 μM for Dihydroclusin diacetate in M12.C3.F6 | Dihydroclusin diacetate was shown to be active against both murine cancer cell lines while ariensin, burseran, were active against only RAW264.7 murine cell line only | [58]      |
| Dihydroclusin diacetate     |                       |                                 |           |                  |                                  |                        |              |                                                                          |           |
| (-)-Hinokinin               | 4                     | Zanthoxylum pistaciaeflorum Hayata, Rutaceae | Methanol  | Stem Bark       | HT-29 cell line                  | 3.52 μg/mL (ED_{50} value) | Dose        | Showed significant cytotoxic activity against HT-29 cell line           | [59]      |
| (-)-Deoxypodophylotoxin, Angeloylpodophylotoxin, Deoxypicropodophyllotoxin, Picropodophyllotoxin | 12, 59, 60, 61 | Anthriscus sylvestris Hoffm., Umbelliferae | Methanol  | Roots            | HL-60                            |                        |              | Compounds have an apoptosis-inducing effect in HL-60 cells and it was determined by caspase-3 activation and DNA fragmentation. Typical ladders of DNA fragmentation were observed when treated with compound angeloylpodophylotoxin, picropodophyllotoxin at 1 mM and (-)-Deoxypodophyllotoxin at 0.01 mM | [60]      |
| Phyllanthusmin A            | 62                    | Phyllanthus oligospermus, Phyllanthaceae | Chloroform fraction of methanol extract | Stems and roots | KB and P-388                  | 2.24 and 0.13 μg/mL |                        | Phyllanthusmin A showed significant cytotoxicity                           | [61]      |
| Name              | Structure ID (Fig. 4) | Source            | Extract       | Part   | Cancer cell line used (In vitro) | IC_{50}  | In vivo | Dose | Comments                                                                 | Reference |
|-------------------|-----------------------|-------------------|---------------|--------|---------------------------------|----------|---------|------|---------------------------------------------------------------------------|-----------|
| (-)-Kusunokinin   | 63                    | 

Piper nigrum, Piperaceae  

Dichloromethane  

Fruits  

MCF-7 and MDA-MB-468  

1.18 and 1.62 µg/mL  

This compound induced cell apoptosis and drove cells toward the G2/M phase which is determined by cell studies. It also decreases topoisomerase II and Bcl-2. There is increase in p53, p21, bax, cytochrome c, and caspase-8, -7, and -3 activities, except caspase-9. This shows that kusunokinin has potent anti-cancer activity through the extrinsic pathway and G2/M phase arrest. | [62] |
| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC_{50} | In vivo | Dose | Comments | Reference |
|------|---------------------|--------|---------|------|--------------------------------|--------|---------|------|----------|-----------|
| Yatein | 13 | Austrocedrus chilensis, Cupressaceae | Methanol | Heartwood | P3X63-Ag8.653 | Yatein exhibited potent cytotoxicity, inducing 75% cell death at 25 mg/mL after 24 h of treatment | Yatein showed toxicity in P3X cells in a dose-dependently. In cells that survived to yatein treatment, the microtubular apparatus was altered, as determined by immunofluorescence techniques, and SEM and TEM analyses displayed changes in morphological and ultrastructural level. There was alteration in cell shape and membrane system was damaged | [63] |
| (-)-Carinol, (-)-Carissanol, and (-)-Nortrachelogenin | 64, 65, 66 | Carissa spinarum L., Apocynaceae | Methanol | Stem | MCF7 and AS49 | <1 µg/mL | 11.0 and 17.4 µg/mL | 29.0 and 88.3 µg/mL | The most active lignan was (-)-carinol and (-)-carissanol was more potent than (-)-nortrachelogenin | [64] |
| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC<sub>50</sub> | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|---------------------------------|----------------|--------|------|----------|-----------|
| Sesamin, Kobusin, 4′O Demethyl magnolin | 67, 68 | Zanthoxylum alatum, Rutaceae | Petroleum ether | Stem bark | A549 and MIA-PaCa | 37.46 ± 1.097 and 34.04 ± 1.7621 | 34.71 ± 2.331 and 32.86 ± 2.0271 | 26.47 ± 1.871 and 26.47 ± 1.871 mg/mL | Cytotoxic activity has been shown by all three isolated lignans in different ranges. 4′O dimethyl magnolin was the novel bioactive compound from a plant source and found to be most active. In apoptosis study, treatment caused typical apoptotic morphological changes. It enhances the apoptosis at IC<sub>50</sub> dose (21.72 mg/mL) on MIA-PaCa cell line. This compound induce apoptosis as the mechanism of cell death | [65] |
| Justirumalin | 69 | Justicia neesii, Acanthaceae | MCF-7, AGS | | | 42.8 and 42.1%, inhibition, respectively | 25 μg/mL | Justirumalin inhibited human stomach and breast cancer cells | | [66] |
| Name                  | Structure ID (Fig. 4) | Source                      | Extract                | Part            | Cancer cell line used (in vitro) | IC₅₀       | In vivo | Dose       | Comments                                      | Reference |
|-----------------------|----------------------|-----------------------------|------------------------|----------------|----------------------------------|-----------|---------|------------|-----------------------------------------------|-----------|
| Justicidin E, Simplexolin | 70                   | Justicia caoriculata, Acanthaceae | Methanol               | Whole plant     | MCF-7, SF-268, CNS, NCI-H460, HCT-116 and AGS | 25 μg/mL  |          |            | Justicidin E inhibited the proliferation of lung, breast and colon cancer cell lines with inhibition values ranged between 40 and 53% and simplexolin gave 40–50% inhibition against lung, breast, colon, and CNS cancer cell lines when tested at 25 μg/mL | [66]      |
| Sylvatesmin           | 72                   | Lancea tibetica Hook. f. et Thoms, Scrophulariaceae | Methanol               | Whole plant     | B16, SMMC-7721, Hela           | 40.4±1.4 mg/mL, 113.4±2.16 mg/mL, 127.9±3.20 mg/mL | 25 μg/mL  |          |            | Sylvatesmin exhibited the effective anti-tumor activity, especially on B16 cells | [67]      |
| Gomisin N             | 73                   | Schisandra chinensis (Turcz) Baill, Schisandraceae or Magnoliaceae | Dichloromethane        | Ripe berries    | HT-29                            | 43 μM      |          |            | Gomisin N was effective against colorectal proliferative processes | [68]      |
| Epieudesmin           | 74                   | Hernandia nymphaeifolia (Presl) Kubitzki, Hernandiaceae | CH₂OH/CH₂Cl₂ (1:1) extract | Fruits          | AS49, MCF-7 and HER2, MDA-MB-231 | 5.7 μM, 8.1 μM, 231 & 2 μM     |          |            | Compounds displayed significant anti proliferative activity | [69]      |
| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC50 | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|----------------------------------|------|---------|------|----------|-----------|
| Podophyllotoxins, Diphyllin, Etoposide (VP–16), teniposide | 12, 75, 76, 77 | Podophyllum peltatum, Berberidaceae | Whole plant | P-388, HT-29, A-549 and MEL-28 | This bioactive lignan is very effective on small cell lung cancer, malignant lymphoma, and testicular carcinoma. It is also potent on Wilms tumors, ovarian cancer, brain tumors, urinary tract cancer, etc. | [70] |
| Liriodendrin | 78 | Plumeria rubra, Apocynaceae | Water soluble fraction of methanolic extract | P-388 murine lymphocytic leukemia and human cancer cell types (fibrosarcoma, melanoma, breast, lung, colon and KB) | P-388—24 µg/mL Fibrosarcoma—98.9 µg/mL Melanoma—19 µg/mL Breast cancer—30 µg/mL Lung cancer—6.0 µg/mL Colon cancer—16 µg/mL KB—6.0 µg/mL (ED50 values) | Exhibit cytotoxic activity | [71] |
| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC$_{50}$ | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|---------------------------------|---------|--------|------|----------|-----------|
| 5'-Methoxydehydro podophyllotoxin, dehydro-β-peltatin methyl ether, Dehydrodehydrpodophyllotoxin, Deoxydehydrpodophyllotoxin, Yatein, 4,4′-Demethyldeoxypodophyllotoxin, Isodeoxypodophyllotoxin, Deoxypicropodophyllin, β-apopicropodophyllin | 79, 80, 47, 81, 13, 82, 83, 60, 84 | Hyptis verticillata, Lamiaceae | Chloroform | Aerial parts | P-388, HT-low, KB, A431, ZR-75-1, LNCaP and U873 | 4.0, 15.6, 6.0, 6.2, > 20, 11.6 and 16.3 µg/mL, 1.8, 3.4, 2.2, > 20, > 20, 3.2, and 5.9 µg/mL, > 5, 9.7, 5.0, > 20, > 20, 11.7 and > 20 µg/mL, > 5, > 20, 11.6 and > 20 µg/mL, 0.4, 0.07, 0.08, > 20, 0.5, 0.16, and 0.3 µg/mL, 0.005, 0.01, 0.01, 0.08, 2.1, 0.02 and 0.1 µg/mL, > 20, 10.7, 6.7, 6.2, 13.2, 12.0 and 2.9 µg/mL, 0.1, 0.2, 0.1, > 20, 0.6, 0.2 and 0.1 µg/mL, 0.002, 0.003, 0.05, 4.3, 2.0, 0.01 and 0.001 µg/mL (ED$_{50}$ values) | > 5, > 20, 11.4, 6.2, > 20, 11.6 and > 20 µg/mL, > 5, > 20, 11.6 and > 20 µg/mL, 0.4, 0.07, 0.08, > 20, 0.5, 0.16, and 0.3 µg/mL, 0.005, 0.01, 0.01, 0.08, 2.1, 0.02 and 0.1 µg/mL, > 20, 10.7, 6.7, 6.2, 13.2, 12.0 and 2.9 µg/mL, 0.1, 0.2, 0.1, > 20, 0.6, 0.2 and 0.1 µg/mL, 0.002, 0.003, 0.05, 4.3, 2.0, 0.01 and 0.001 µg/mL (ED$_{50}$ values) | [72] |

Wikstromol 8S | Wikstroemia foetida var. oahuensis and Wikstroemia uwa-ursi Gray | Chloroform | Fraction of ethanolic extract | Whole plant | P-388 lymphocytic leukemia (3PS) test system | 16, 10, 4, 2, and 1 mg/kg | Wikstromol demonstrate activities of 154, 146, 137, 141, and 130% test/control at dose of 16, 10, 4, 2, and 1 mg/kg respectively | [73] |
### Table 1 (continued)

| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC₅₀ | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|----------------------------------|------|---------|------|----------|-----------|
| 4′-Demethoxy-3′,4′-methylenedioxy-methyl roccaglate | 86 | *Aglaia elliptica* Bl., Meliaceae | Chloroform | Stem | HT-1080, KB, A431, LNCaP, ZR-75-1, and U373, BCI | 10.0, 6.0, 10.0, 2.0, 2.0, 0.8, 0.9 ng/mL | Antitumor potential of compound was performed with female Balb/c athymic nude mice. Compound significantly inhibited the growth of BCI cells in culture. The growth of tumor was retarded by treatment with isolated compound during the first 23 days of the study, but after that tumor growth paralleled to the control group | This compound acts by cytostatic mechanism, rather than inducing necrosis or apoptosis. Cells were transiently blocked in the G1/G0 phases of the cycle, and this may be due to inhibition of protein biosynthesis | [74] |
| 4,5-Didemethylpodophyllotoxin 7′-O-b-D-glucopyranoside | 87 | *Sinopodophyllum emodi*, Berberidaceae | n-butanol | Roots and rhizomes | Hela, K562, SH-SYSY and CNE | Compound showed cytotoxicity against four human cancer cell lines | | |
| Ramonanin A | 88, 89 | *Guaiacum officinale*, Zygophylaceae | Chloroform | Heartwood | MD-MBA 231 | 18 μM | The ramonanins exhibit cytotoxic activity against human breast cancer cell lines with an IC₅₀ value of 18 μM and induce cell death via apoptotic mechanisms | Ramonanin A-treated MD-MBA 231 cells showed characteristic features of apoptotic cell death, which appeared in a time and dose-dependent manner and cell cycle distribution was monitored via flow cytometry using fluorescence-activated cell sorting. It was noted that the ramonanins strongly disrupt cell cycle progression at the G1/S phase transition | [76] |
| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC$_{50}$ | In vivo | Dose | Comments | Reference |
|------|----------------------|--------|---------|------|--------------------------------|--------|--------|------|----------|-----------|
| Ligraminol A, Ligraminol C, Ligraminol D | 90, 91, 92 | Acorus gramineus, Araceae | Methanol | Rhizomes | A549, SK-OV-3, SK-MEL-2 | 6.92, 9.44, and 4.53 μM | Compounds showed weak inhibitory activity against various cancerous cell lines. Study has also been performed to check whether the cytotoxicity was selective between tumor and normal cells. For this compounds were evaluated for normal human cell line, HUVEC. This was noted that cytotoxicity of isolated compounds was higher against tumor cells than normal cells. Ligraminol A showed the highest selective cytotoxicity against the SK-MEL-2 cell | [77] |
| Neglignan H | 93 | Schisandra neglecta, Schisandraceae | Ethyl acetate layer of 70% aqueous acetone | Stem | NB4, A549 and MCF7 | 8.1, 7.4 and 6.7 μM | | | | [78] |
| Linderanosides A and B | 94, 95 | Lindera glauca, Lauraceae | Methanolic | Twigs | A549 | 20.86 ± 0.94, 21.85 ± 0.61 μM | | | | [79] |
| Name                        | Structure ID (Fig. 4) | Source                  | Extract        | Part  | Cancer cell line used (in vitro)                              | IC<sub>50</sub> | In vivo Dose | Comments                                                                 | Reference |
|-----------------------------|----------------------|-------------------------|----------------|-------|---------------------------------------------------------------|----------------|--------------|--------------------------------------------------------------------------|-----------|
| Tiliamuroside, Schizandriside | 96, 97               | Tilia amurensis Rupr., Tiliaceae | Methanolic Trunk |      | AS49, SK-OV-3, SK-MEL-2, and HCT-15                          | 7.32, 8.89, 7.84, 6.18 μM | 6.90, 5.88, 3.26, 6.65 μM | cytotoxic activity of compounds against the tested cell lines were due to absence of a methoxy group at C-3 in the aryl-tetralin type lignan as indicated by the results | [80]      |
| Pronaphthalide A, Procumbenoside J, 6′-hydroxyl justicidin A, 6′-hydroxyl justicidin B, Tuberculatin | 98, 99, 100, 101, 102 | Justica procumbens, Acanthaceae | Ethanol Whole plants |      | Human LoVo and BGC-823                                        | 0.03–10.0 μM, |             | Cleistantoxin had strong activity against KB cells also showed significant activity against MCF-7 and MCF-7R | [81]      |
| Cleistantoxin               | 103                  | Cleistanthus indochinensis, Euphorbiaceae | Dichloromethane |      | KB, MCF-7, MCF-7R                                            | 0.022, 0.036, 0.014 μM |             |                                                                 | [82]      |
### Table 1 (continued)

| Name                | Structure ID (Fig. 4) | Source         | Extract                  | Part                  | Cancer cell line used (in vitro) | IC<sub>50</sub> | In vivo | Dose | Comments                                                                 | Reference |
|---------------------|----------------------|----------------|--------------------------|-----------------------|---------------------------------|-----------------|---------|------|---------------------------------------------------------------------------|-----------|
| Phyllanthusmin D    | 104                  | *Phyllanthus poilanei*, Phyllanthaceae | Chloroform fraction of methanol extract | Air-dried leaves, twigs, flowers and fruits | HT-29                            | 170 nM          | Compound showed activity when tested in an in vivo hollow fiber assay using HT-29 cells implanted in immunodeficient NCr nu/nu mice | 5 μM      | Cytotoxic effects of phyllanthusmin D were by inducing tumor cell apoptosis through activation of caspase-3. DNA topology activity was not inhibited. Treatment of HT-29 cells with phyllanthusmin D for 72 h resulted in 28.2% or 30.3% of HT-29 cells undergoing early apoptosis, respectively. | [83]      |
| Heilaohulignan C    | 105                  | *Kadsura cocinea*, Schisandraceae | 80% ethanol | Roots | HepG-2, BGC-823 and HCT-116 | 9.92, 16.75 and 16.59 μM | | | Heilaohulignan C showed good cytotoxicity in HepG-2 cancer cells and weak cytotoxicity against BGC-823 and HCT-116 cancer cells | [84]      |
| (-)-Cubebin         | 106                  | *Piper cubeba*, Piperaceae | Acetone | Seeds | A549, K562, SiHa, KB | 8.30 ± 0.16, 8.66 ± 0.43, 8.16 ± 0.41 μM | | | (-)-Cubebin displayed potent inhibitory effect against gastric and lung carcinoma | [85]      |
| Hedyotol-B          | 107                  | *Herpetospermum pedunculosum*, Cucurbitaceae | Ethyl acetate | Stems | SGC7901, AS49 | 1.7 ± 0.1 and 6.1 ± 0.5 μM | | | Hedyotol-B displayed potent inhibitory effect against gastric and lung carcinoma | [86]      |
Table 1 (continued)

| Name | Structure ID (Fig. 4) | Source | Extract | Part | Cancer cell line used (in vitro) | IC₅₀ | In vivo | Dose | Comments | Reference |
|------|-----------------------|--------|---------|------|--------------------------------|------|--------|------|----------|-----------|
| Bizanthplanispine A and B, Zanthpodocarpin A and B, Planispine A | 108, 109, 110, 111, 112 | Zanthoxylum planispinum Sieb., Rutaceae | 95% aqueous MeOH | Roots | Hela, HL-60, PC-3 | Bizanthplanispine A and B, zanthpodocarpin A and B, Planispine A showed significant reduction in the proliferation of Hela with IC₅₀ values ranging from 15.00 to 26.44 µg/mL. Planispine A showed the strongest inhibition on the growth of Hela and PC-3 with IC₅₀ values of 4.90 and 23.45 µg/mL. | All isolated compounds showed inhibitory effect on different cancer cell lines | [87] |

L5178Y, leukemia mouse lymphoma cells; MCF-7, breast cancer cell lines; HCT116, human colon carcinoma cell lines; P-388, breast cancer cells; SK-BR-7, breast cancer cells; MDA-MB-231, breast cancer cells; MDA-MB-435s, breast cancer cells; LNCaP, prostate cancer cells; COC1, ovarian cancer cells; K562, human chronic myeloid leukemia; HT1080, human fibrosarcoma cells; KB16, human epidermoid carcinoma cells; HT-29, human colorectal adenocarcinoma cell line; A549, human lung cancer cell line; SK-Mel-2, human skin melanoma cell line; B16F1, mouse melanoma cell lines; T98G, human glioblastoma cell line; U87MG, human glioblastoma cell line; U251, human glioblastoma cell line; U118, human glioblastoma cell line; U251MG, human glioblastoma cell line; U373, human glioblastoma cell line; SW13, human breast cancer cell lines; Hela, human uterine cervix carcinoma cell line; HL-60, human acute promyelocytic leukemia cell line; HepG2, human hepatocellular carcinoma cell line; Bel-7402, hepatocellular carcinoma cell line; Hep-2, human epidermoid carcinoma cell line; E09, human umbilical vein cell line; HeLa, human uterine cervix carcinoma cell line; L929, murine fibroblast cell line; RAW 264.7, murine macrophage cell line; HT-15, human colorectal adenocarcinoma cell line; SW480, colon carcinoma cell line; J86, murine epidermal cells; CCRFCEM, leukemia cell line; K-562, leukemia cell line; MOLT4, leukemia cell line; RPMI-8226, leukemia cell line; SMMC-7721, human hepatoma cell line; V79, hamster lung fibroblast cell line; B16, mouse melanoma cell line; M12.C3.F6, murine cancer cell line (macrophages transformed by virus) Abelson leukemia; MDA-MB-468, breast cancer cell lines; P3X63-Ag8.653, murine myeloma cell line; AGS, gastric cancer cell lines; Mia-PaCa, pancreatic carcinoma cell line; SMMC-7721, human hepatoma cells; HER2, negative breast cancer cell line; MDA-MB-231, triple negative breast cancer cell line; MEL-28, melanoma cell line; HT-1080, Human fibrosarcoma cells; KB, human oral squamous carcinoma; A431, human epidermoid carcinoma; ZR-75-1, human hormone-dependent breast cancer; U373, human glioblastoma cell line; BCL, human breast cancer; SH-SY5Y, neuroblastoma cell line; CNE, nasopharyngeal carcinoma cell line; SK-OV-3, ovary malignant ascites; NB4, human acute promyelocytic leukemia cell line; MCF-7R, human breast cancer cell line; SiHa, human cervical carcinoma; SGC7901, human gastric carcinoma; PC-3, human prostate carcinoma cells; SCLC, small-cell lung cancer;
Acknowledgements
We express our sincere thanks to Management of the institute for providing facilities.

Author contributions
MM participated in conceptualization and writing of the manuscript. BCJ, PSB contributed in editing. AB, ANS review the final version of article. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 28 January 2022   Accepted: 17 May 2022

Published online: 04 June 2022

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