Chapter

# Plant-Derived Compounds against Microbial Infections and Cancers

*Gabin Thierry M. Bitchagno, Vaderament-A. Nchiozem-Ngnitedem, Nadine Tseme Wandji, Guy Cedric T. Noulala, Serge Alain T. Fobofou and Bruno Ndjakou Lenta*

## Abstract

Plants synthesize and preserve a variety of metabolites known as natural products. Many of them are easily extractable and can be used as starting material or chemical scaffolds for various purposes, especially in drug discovery. Numbers of reports have listed valuable candidates with privilege scaffolds currently in active development as drugs. New compounds with anticancer and antiinfective activities have been discovered recently, some presented these backbones. The present book chapter aims to highlight these findings from plants which can be considered valuable for the development of new drugs against malignant cells and infective diseases. Interest in anti-infective agents is increasing due to the resistance of microorganisms to existing drugs and newly emerging infectious diseases. This resistance is also, nowadays, associated to some forms of cancers. In addition, the value of plants as essential part in the health care pipeline in low- and middle-income countries is under consideration even though these countries are almost all surrounded by a rich and untapped biodiversity. People are always relying on "modern drugs and treatment" which is unfortunately not affordable to all. Therefore, the present compilation of data on plant-derived compounds can inspire the formulation of ameliorated traditional medicines (ATM) against the targeted diseases and the conservation of species.

**Keywords:** phytoconstituents, anticancer, antimicrobial, biological cutoff points, sesquiterpenoid lactones, phenolic compounds

## 1. Introduction

### 1.1 General statement

As any other organisms on Earth, plants are said to possess multi-functional properties. They constitute feedstock materials to feed people and are reputed for their uses in medicines [1, 2]. History of plants has been always related to that of Human. Reports said Human have always insured their primary health care by using plants [3–5]. Even with the discovery of technology leading to synthetic drugs with sometimes more efficiency, plants still remain ubiquitous and safe for health concerns.

Research currently overflows in the literature related to the chemistry and biology of plants. Interests focus on experimental validation of ethnopharmacological uses of certain herb and formulation of plant extracts for a sustainable health care [1–5]. Therefore, plants are ground, exhausted and evaluated for various biological activity including properties to inhibit the growth of or to kill microorganisms and tumor cell lines. However, both microorganism and cancer cells become more and more resistant and remain serious threats for life. As an example, resistance to penicillin used for the treatment of lung infection ranged from 0 to 51% around the World and between 8 and 65% *Escherichia coli* associated with urinary tract infections presented resistance to ciprofloxacin, another antibiotic (https://www.who.int/health-topics/antimicrobial-resistance). WHO took some measures to diagnose and eradicate the issue but the problem is still actual and present.

More than half of existing antibiotics and anticancers are from synthesis of which almost a quarter takes its origin in natural substances isolated from plants, marine organisms and microorganisms [6]. Nevertheless, plant supply extracts continue to play a relevant role in human beings daily life. Up to date data show that plant extracts are reputed in food science where they are used as dietary supplements [6–8]. This practice is prevalent in Europe and North America where the interest in plants and related materials is rising up. Despite the progress made in the field of the synthesis of active principles for the formulation of medicaments, people still rely on natural occurring drugs due to their safety and uniqueness. The list of valuable substances from plants cannot be exhaustive.

In ancient time, the discovery of salicin, an *ortho-O*-glucopyranosylphenylethanol, from *Salix alba* led to the development of the reputed anti-inflammatory agent aspirin [9, 10]. Morphine, a benzylisoquinoline alkaloid isolated from *Papaver somniferum*, is a painkiller quite known in medicine and which also exist under its derivatives, heroin and codeine [9, 10]. Another alkaloid namely quinine isolated from *Cinchona succirubra* has been for long employed to cure malaria and fever related ailments but since 2004, almost all antimalarial drugs in the markets is made up of artemisinin isolated from the Chinese medicinal plant *Artemisia annua*. Artemisinin is commercialized under various acronyms including arteether, artesunate or artemether [10, 11]. In other hand, the chemotherapy of breast cancer uses the drug taxol which is the commercial name for paclitaxel, a diterpene isolated from *Taxus brevifolia*. Other compounds like ingenol-3-angelate, from *Euphorbia peplus*, known under the acronym Ingenol mebutate or the L-histidine-derived alkaloid pilocarpine found in *Pilocarpus jaborandi* are also some drugs used against other form of cancer [12–14].

Days after days, we keep discovering the deeply wealth of our surrounded nature. Reports abound in the literature especially on valuable natural compounds in drug development [6–8]. Most of them highlight natural product scaffolds as building blocks to the development of other compounds through synthesis [6–8]. A list of priority backbones has even been proposed to lead the development of new drugs [6].

However, interest in health care could also be to find out natural occurring compounds with considerable effects and low toxicity which can be introduced in the actual pipelines of treatment of a disease. That is, the sensibility of the found natural substance is not strong enough to compete commercial drugs but could be proposed alongside prescribed medicines because of its safety and availability. This can actually help in low- or middle-income countries to face certain diseases and build up a sustainable health care system. One can question how useful was the discovery of artemisinin for indigenous people if they have to wait years for pharmaceuticals companies to manufacture the drugs before its consumption. The same interrogation can also be valid to other discovery from plants, e.g. taxol,

michellamine B or vinblastine. The plant sources of these active substances are known but still people from villages are waiting for "modern medicines" to take care of their respective health problems.

### 1.2 Problematic of microbial infections nowadays: drug resistance and climate change

According to WHO microbial infections are said to be the second cause of death globally, with low- and middle-income countries bearing the greatest burden. They include bacteria or fungi but viruses and protozoa diseases are also listed in this category (https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance). Their origin preceded that of human life on earth [15]. In fact, human comes from successive mutations and evolution of bacteria [15]. Our body is made up of more than 100 trillion bacteria [16–18]. Some of them are useful in human life where they played a critical role in metabolism. However, greater percentage of them has been found to be harmful. By analogy to what is being said by believers, "you are dust and will return to dust," one can also argue that "you are bacteria and will return bacteria."

A lot of concerted effort has been put forward since the existence of mankind in trying to understand the biology of infective pathogens and their control. Some success has been achieved although there still more room for further research on this area. Through our constant manipulation and uses of these pathogens together with huge amount of chemicals, including drugs, we end up developing "new organisms" with different properties compared to their natural counterparts. In fact, the original pathogens start developing resistance to the drugs that were previously used for their eradication, making the problem worse [19–22].

The question of resistance of pathogens to commercialized drugs relies on the living environment of these small organisms. A misconception of bacteria considered that they exist as individual organisms [23]. However, things are different. Bacteria accumulated in colonies to live. They generally stick on a surface and gathered to survive together [23, 24]. Such a constitution known as biofilm is made up of bacteria somehow wrapped in a certain liquid (extracellular matrix) with strange properties. The entire constitution acts as a safety membrane for bacteria. The so-described making-up of this living organism constitutes the first barrier to bacteria and therefore the first stage of resistance [25, 26]. Biofilm are quite distributed in hospitals and nursing homes. They are claimed in household and industrial pipes, biomaterials such as contact lenses, medical devices including implants and urinary catheters, as well as plant and animal tissues. Cases of bacteria resistance have exploded this last decade especially in those zones [23–26]. This includes bacteria like *Acinetobacter*, *Pseudomonas* and various *Enterobacteriaceae* (*Klebsiella*, *E. coli*, *Serratia* and *Proteus*) which cause severe and often deadly infections such as bloodstream infections and pneumonia. Bacteria are carried over by devices such as ventilator systems and blood stream catheters. In high-income countries, 7% of all hospitalized people will contract some form of infection, including one in three people in intensive care units. In low- and middle-income countries, this figure rises to at least 10% of hospitalized people, and up to half of people in intensive care units, said the WHO (https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

The World is currently facing an unprecedented rising of temperature, leading to certain change in habits and behavior. Discussion are mainly focused on how it could have an impact on human life, as it's getting colder and colder when it is the cold season or more and more hot when it is the hot season or even hot when it is supposed to be cold and vice versa. Politics in every country recommend adopting

new habits to stop the rising up of the earth temperature. In the meantime, it seems that no one is caring about changes occurring at microorganism scale. It comes out that changes occurring in microorganisms due to climate change are not so important for us. And yet we should beware at least, the occurrences of the new viruses Ebola and Corona these last years should make us change our mind on how the World is changing. New microorganisms would be discovered, and the existing microorganisms could mutate to more harmful organisms. Fortunately, almost the same changes are also expected in plant kingdom even though the global warming and deforestation contribute also to plant extinctions. It is also awaited that new metabolites are being made as a result of new biosynthetical routes. These metabolites could either be directly active against pathogenic microorganisms or inspire new synthetical routes in laboratories to reach new drugs and medicines.

### 1.3 Standard antibacterial and anticancer cutoff points

Discussions are ongoing in the literature between scientists to clearly established standards for a substance to be considered for further steps in drugs development. Established standards are rare or inaccessible. The Kuete's group proposed standards of evaluating antimicrobial or anticancer properties of secondary metabolites derived from plants. They established that the antimicrobial activity of a crude extract can be considered significant when it MIC is below 100 μg/mL, moderate when between 100 and 625 μg/mL and low when more than 625 μg/mL. For pure compounds, the activity is considered significant when the MIC is below 10 μg/mL, moderate when between 10 μg/mL < MIC<100 μg/mL or low when greater than 100 μg/mL. One can notice that these standards are not considering the MIC of standard commercial drug references. We are not saying that the comparison of obtained MIC with those of the commercial drug is not necessary but the abovementioned cut-off points precise the ranges for a plant substance to be considered as valuable in drug discovery. Likewise, an extract is said to possess a good cytotoxicity if the $IC_{50}$ values are below 4 μg/mL, modererate when 4 < $IC_{50}$ < 20 μg/mL/10 < $IC_{50}$ < 50 μM and low with $IC_{50}$ above 100 μg/mL (250 μM) [14, 15]. While for cancer cell lines the activity of the pure compound is consider strong when $IC_{50}$ < 10 μM [20, 21].

Another point of constant intensive discussion remains the relative low activity of most plant extracts and related constituents against microbial and cancer strains. Their activities are sometimes hundred- or thousand-fold less than the sensitivity of existing drugs. Some scientists find these activities not significant enough to be considered for clinical trials as a phytochemical substance should show comparable sensitivity with the commercial drugs. However, knowing that most cancer treatments are based on chemotherapy which is, as known, as harmful as the disease, can natural substances replace synthetic compounds? Likewise, one can also question infectious disease treatments in the same words. In what extent can we clearly consider a plant based products in drug development with respect to their activity against strains of bacteria or tumor cell lines? As mentioned above, the objective is not to compete with existing drugs developed with many expenditures but simply to select valuable extracts and phytoconstituents which could be used alongside actual treatments because of their safety and availability status especially for less developing countries.

### 1.4 World sustainable development goals related to the field

In September 2015, the UN adopted a list of 17 goals for a better life on the planet with emphasis on the quality of life for posterity (https://sustainabledevelopment.

un.org/?menu=1300). Globally it is recognized that ending poverty and other deprivations must go hand-in-hand with strategies that improve health and education, reduce inequality, and spur economic growth, by tackling climate change and working to preserve our oceans and forests are essential for our future as human beings. In the health sector, people should commit themselves to promote healthy lively hood and well-being for all at all ages. These are objectives stated in the Sustainable Development Goal number 3 of the list. Targets within this goal include ending the preventable deaths of newborns and children and ensuring access to effective medicines to all.

However, we are still living in a place where basic infections (malaria, typhoid, diarrhea, cholera and others) can cause death; a World where medicines are too expensive and inaccessible to everyone; a region where people have to walk more than 10 Km to expect treatment in a hospital or a World with increasing political and economic crisis. Nowadays, one should also highlight the increasing resistance of microbes and other pathogens to existing drugs and the occurrence of new strains of bacteria and virus. The former has been related to the overuse and misuse of drugs which modify the living pathogens environment making them used to it, thus developing tolerances to the used drugs.

One of the alternatives to tackle these challenging issues remain natural remedies and drugs. Many sources are being investigated but plants remain the most exploited. Substances from plants are quantitative, affordable, reachable and biologically recognized and easily metabolized by other organisms. They are environmentally friendly and can thus be promoted ever. Numbers of reports are available in the literature, highlighting the antimicrobial and anticancer properties of phytoextracts and products. Extracts can then be standardized and proposed to our fellow population to alleviate the cost of various and diverse drugs available in the markets.

### 1.5 Rationale of this survey

The present research literature aims to review recent plant compounds reported for their anticancer or antimicrobial properties which constitute valuable candidates to drug development. Our survey covers research reported from 2010. We only listed compounds with MICs or $IC_{50s} < 10$ μg/mL for a molarity scale ranging from $10^{-6}$–20 μM. Activities of extracts were not highlighted herein. Both sensitive and resistant strains were checked out without restriction.

## 2. Plant-based secondary compounds with antimicrobial properties

Infective diseases are one of the most common illnesses in the World. They are currently the main concern on earth due to the ongoing Coronavirus (Covid-19) outbreak. Some pathogens spread out in animals and much of them are not known so far. But, at one moment or at another, due to our growing familiarization with wild animals, pathogens can spread within Human kingdom. Research are constantly been done to contain the diseases and come over the pathogens. Most of them are based on drug discovery, one of the oldest fields of Human concern so far. Plants constitute the main source of drugs although interests have moved to bioactive microbial constituents in the last decades mainly against microbial infectious. Owing to the rich biodiversity in our planet, the search for bioactive compounds from untapped natural resources is among the important ongoing projects.

One of the main constituents of plants with pronounced therapeutic interests against infective diseases are volatile oil. They are found in almost every organ of a

plant but are said to be present in high extent in fruits and seeds. The composition of essential oil consists of monoterpenes and sesquiterpenes paired with aromatic compounds and lightweight esters, fatty acids, alcohols, ketones and aldehydes. Some examples include $\gamma$-terpinene, carvacrol, $p$-cymene, thymol, linalool, $\alpha$-terpinene, limonene, eucalyptol, geranyl propionate and $\alpha$- and $\beta$-pinene [27]. Owing to their high hydrophobicity, essential oil are said to impair the cell membrane of microbes, increase their membrane permeability and decrease their cytoplasmic pH [28]. The so-described abilities explained their significant activity against bacteria and fungi including resistant strains like *Staphylococcus sp*. and *Pseudomonas sp*. with MIC values approaching 0.01 μg/mL [27]. Volatile oil play also an essential role in protecting and even preventing biofilm development which is very important as presented above [29]. However, the same lipophilicity capacity of essential oil, relevant for their good antiinfective properties, constitutes also their

| Family | Species (part) | Compound name | Test microorganisms (MIC in μg/mL) | Refs. |
|---|---|---|---|---|
| *Guttiferae* | *Garcinia mangostana* | Mangostin A (**1**) | MRSA (6.25 μg/mL), VRE (3.13 μg/mL) | [30] |
| | *Garcinia cowa* (fruits) | | *B. cereus* (0.5 μg/mL), *B. subtilis* (0.25 μg/mL), *M. luteus* (1.0 μg/mL) | [31] |
| | *Garcinia mangostana* | Mangostin Y (**2**) | MSSA (6.25 μg/mL), MRSA (3.13 μg/mL), VRE (6.25 μg/mL), VSE (6.25 μg/mL) | [30] |
| | *Garcinia cowa* (stem barks) | Cowanol (**3**) | MRSA SK1 (2 μg/mL), *S. aureus* (8 μg/mL) | [32] |
| | | Cowagarcinone E (**4**) | MRSA SK1 (8 μg/mL) | |
| | | Garciniacowone (**5**) | MRSA SK1 (2 μg/mL), *S. aureus* (2 μg/mL) | |
| | | Cowanin (**6**) | MRSA SK1 (4 μg/mL) | |
| | *Garcinia cowa* (fruits) | | *B. subtilis* (4 μg/mL), *M. luteus* (4 μg/mL) | [31] |
| | *Garcinia cowa* (fruits) | Garcicowanone A (**7**) | *B. cereus* (0.25 μg/mL), *B. subtilis* (2 μg/mL), *M. luteus* (4 μg/mL), | |
| | | 9-Hydroxycalabaxanthone (**8**) | *B. cereus* (8 μg/mL), *B. subtilis* (2 μg/mL), *M. luteus* (4 μg/mL), | |
| | | B-mangostin (**9**) | *B. cereus* (0.25 μg/mL), *B. subtilis* (4 μg/mL) | |
| | | Cowagarcinone E (**10**) | *B. cereus* (4 μg/mL), *B. subtilis* (4 μg/mL), *M. luteus* (8 μg/mL) | |
| | | Rubraxanthone (**11**) | *B. cereus* (2 μg/mL), *B. subtilis* (1 μg/mL), *M. luteus* (2 μg/mL) | |
| | *Garcinia smeathmannii* (stem barks) | 1,3,5,8-Tetrahydroxy-2- (3-methy but-2-enyl)-4- (3,7-dimethylocta-2,6- dienyl) xanthone (**12**) | *E. faecalis* (8 μg/mL) | [33] |
| | | Cheffouxanthone (**13**) | *E. faecalis* (8 μg/mL) | |
| | | Ananixanthone (**14**) | *E. faecalis* (2 μg/mL) | |

| Family | Species (part) | Compound name | Test microorganisms (MIC in μg/mL) | Refs. |
|---|---|---|---|---|
| Clusiaceae | *Allanblackia gabonensis (fruits)* | Morelloflavone (**15**) | ATCC8739 (8 μg/mL) | [34] |
| Myristicaceae | *Pycnanthus angolensis (roots)* | Pycnanthulignene A (**16**) | MRSA (9.8 μg/mL) | [35] |
| | | 3,4-Dimethoxy-3′,4′-methylenedioxy-7,7′-epoxylignan (**17**) | *M. smegmatis (9.8* μg/mL) | |
| | | 4,5-Dimethoxy-3′,4′-methylenedioxy-2,7′-cycloligna-7,7′-diene (**18**) | *M. tuberculosis (9.8* μg/mL) | |
| Dioscoreaceae | *Dioscorea bulbifera* (Bulbil) | Bafoudiosbulbins C (**19**) | *M. smegmatis* ATCC700084, *M. tuberculosis* ATCC27294 and *M. tuberculosis* MTCS2 (8 μg/mL) | [36] |
| Clusiaceae | *Garcinia nobilis* (stem bark) | 4-Prenyl-2-(3,7-dimethyl-2,6-octadienyl)-1,3,5,8tetrahydroxyxanthone (**20**) | *M. tuberculosis* ATCC27294 and *M. tuberculosis* MTCS2 (8 μg/mL) | [37] |
| Moraceae | *Dorstenia manii* (roots) | Dorsmanin C (**21**) | *P. aeruginosa* PA 01 and *E. coli* ATCC 10536 (4 μg/mL) | [38] |
| | | Dorsmanin F (**22**) | *P. aeruginosa* PA 01 and *E. coli* ATCC 10536 (4 μg/mL), *K. pneumonia* PA01 (8 μg/mL) | |
| | | Dorsmanin E (**23**) | *Candida albicans* TCC9002 (8 μg/mL) | |
| | *Ficus exasperata* (stem bark) | (S)-(−) Oxypeucedanin hydrate (**24**) | *B. cereus* (9.76 μg/mL) | [39] |
| | | (R)-(+) Oxypeucedanin hydrate (25) | | |
| | *Trilepisium madagascariense* (stem bark) | Dihydrokaempferol (**26**) | *E. coli* ATCC8739 (8 μg/mL) | [40] |
| Rutaceae | *Fagara tessmannii* (roots) | Bergenin (**27**) | *E.*AG102 and *K. pneumoniae* ATCC 11296 (4 μg/mL) *E. coli* ATCC 8739, *K. pneumoniae* ATCC 11296, *K. pneumoniae* KP 55, *P. stuartii* PS 299645 and *P. aeruginosa* PA01 (8 μg/mL) | [41] |
| Hypericaceae | *Harungana madagascariensis* (bark) | Ferruginin (**28**) | *E. coli* ATCC 10536, *K. pneumoniae* K2 and *E. cloacae* BM 67 (4 μg/mL) *E. aerogenes* ATCC 13048, *E. aerogenes* EA 294, *P. aeruginosa* PA01 and *K. pneumoniae* KP 55 (8 μg/mL) *K. pneumonia* ATCC 11296, *E. cloacae* BM 47 and *E. coli* ATCC 8739, *E. aerogenes* ATCC 13048, *K. pneumoniae* KP 55, *P. stuartii* (8 μg/mL) | [42] |
| Fabaceae | *Erythrina sigmoidea* (leaves) | Neobavaisoflavone (29) | *E. coli* ATCC 8739, *E. cloacae* ECC 169, *K. pneumoniae* KP 55, *P. stuartii* NAE16 and | [43] |

| Family | Species (part) | Compound name | Test microorganisms (MIC in μg/mL) | Refs. |
|---|---|---|---|---|
| | | | *P. aeruginosa* PA01 (8 μg/mL) *P. stuartii* ATCC 29916, *E. cloacae* BM 47 (4 μg/mL) | |
| Moraceae | *Milicia excels* (roots and leaves) | 2-(3,5-Dihydroxyphenyl) benzofuran-5,6-diol (**30**) | *E. coli* ATCC 8739, *K. pneumonia* ATCC 11296, *E. cloacae* BM 47 (4 μg/mL) *E. coli* AG 102 and *K. pneumoniae* KP 55 (8 μg/mL) | [44–46] |
| | | Candidone (**31**) | | |
| Myristicaceae | *Myristica fragrans* (seeds) | 3′,4′,7-Trihydroxyflavone (**32**) | *E. coli* ATCC 8739 (8 μg/mL) *P. stuartii* ATCC (199645) (4 μg/mL) | [47, 48] |
| Hypericaceae | *Hypericum roeperianum* (stem Bark) | 1,4,6,7-Tetrahydroxyxanthone (**33**) | *P. aeruginosa* PA01 (2 μg/mL) | [49] |
| Fabaceae | *Entada abyssinica* (leaves) | Entadanin (**34**) | *S. typhimurium* (1.56 μg/mL) | [50] |
| | | Quercitrin (**35**) | *S. typhimurium* (3.12 μg/mL) | |
| Meliaceae | *Pseudocedrela kotschyi* (stem bark) | 3,4-Secotirucalla- 4 (28),7,24-trien-3,21- dioic acid (**36**) | *S. aureus* (4 μg/mL) | [51] |
| | | 3,4-Secotirucalla- 4 (28),7,24-trien-3,21- dioic acid (**36**) and 3- methyl ester 3,4- secotirucalla-4 (28),7,24- trien-3,21-dioic (**37**) (1:1) | *S. aureus* (8 μg/mL) | |
| Rubiaceae | *Crossopteryx febrifuga* (stem bark) | l8-epi-3*β*-D-Glucopyranosylurs- l2,20 (30)diene-27,28- dioic acid (**38**) | *K. pneumoniae* ATCC11296 (8 μg/mL) | [52] |
| Lamiaceae | *Leucosceptrum canum* (aerial part) | 4-En-3-keto-stigmasterol (**39**) | *M. luteus* (9.5 μg/mL) | [53] |
| | | Stigmast-5-en-3-acetate (**40**) | *M. luteus* (4.2 μg/mL) | |
| | | 4′,5,7-Trihydroxy-6 methoxyflavone (**41**) | *M. luteus* (6.5 μg/mL) | |
| | | Leucoperoxyterpene (**42**) | *M. luteus* (5.4 μg/mL) and *S. minor* (5.4 μg/mL) | |
| Caryophyllaceae | *Silene rubella* (aerial part) | Oleanolic acid (**43**) | VRE (6.36 μg/mL) | [54] |
| Fabaceae | *Entada abyssinica* (leaves) | Ursolic acid (**44**) | *B. cereus* (6.25 μg/mL) | [55] |

*Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin resistant Enterococcus (VRE), methicillin-sensitive Staphylococcus aureus (MSSA), vancomycin-sensitive Enterococcus (VSE), Staphylococcus aureus (S. aureus), Bacillus subtilis (B. subtilis), Bacillus cereus (B. cereus), Micrococcus luteus (M. luteus), Mycobacteria smegmatis (M. smegmatis), Mycobacteria tuberculosis (M. tuberculosis), Pseudomonas aeruginosa (P. aeruginosa), Escherichia coli (E. coli), Klebsiella pneumonia (K. pneumonia), Candida albicans (C. albicans), Bacillus cereus (B. cereus), Escherichia coli (E. coli), Klebsiella pneumoniae (K. pneumoniae), Providencia stuartii (P. stuartii), Pseudomonas aeruginosa (P. aeruginosa), Enterobacter cloacae (E. cloacae), Enterobacter aerogenes (E. aerogenes), Salmonella typhimurium (S. typhimurium), Staphylococcus aureus (S. aureus), Micrococcus luteus (M. luteus), Streptococcus minor (S. minor), Vancomycin resistant Enterococcus (VRE).*

**Table 1.**
*Examples of plant-based natural products with significant antiinfective properties.*

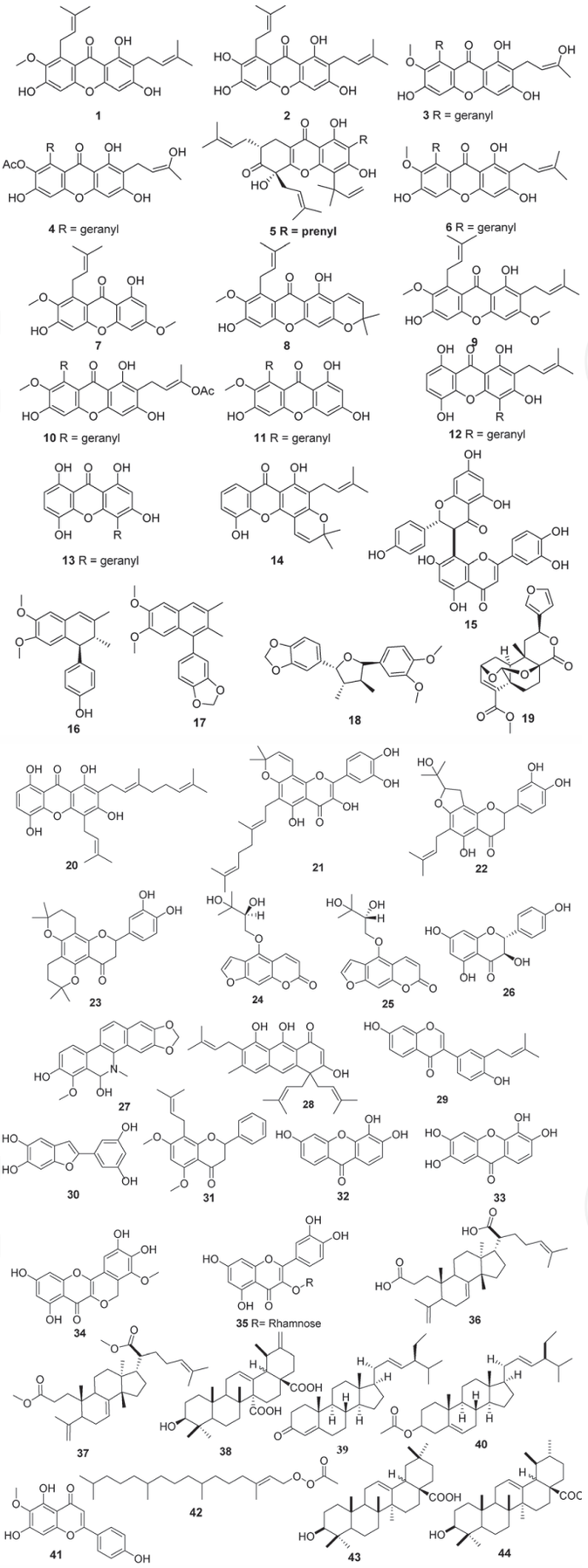



**Figure 1.**
*Bioactive compounds against infective bacteria and fungi.*

main bottlenecks in drug development because essential oil present a low bioavailability. But when isolated, some of their constituents are water soluble e.g. 1.25 mg/mL at 25°C for carvacrol (https://pubchem.ncbi.nlm.nih.gov/compound/carvacrol#section=Solubility) or 1.59 mg/mL at 25°C (https://pubchem.ncbi.nlm.nih.gov/compound/6549) for linalool and are being studied and used as excipient in drug formulation. Essential oil are however reputed in therapies which promoted local application, inhalation or bath modes of treatment like aromatherapy [27, 56]. They are associated to numerous of ailments including depression, indigestion, headache, insomnia, muscular pain, respiratory problems, skin ailments, swollen joints or urine complications [56]. Unlike essential oil, secondary metabolites mainly found in the solid part of a plant extract can present significant activities with considerable bioavailability and hence, constitute the main research object in natural product domain.

Since 2010 at least 44 metabolites have been reported with MIC values below 10 μg/mL. Phenolic compounds (**1–18**, **20–26**, **28–35**, **41**) were the group of compounds mostly active among the metabolites found. Besides, benzophenanthridine (**27**), steroids (**36–37**, **40**), pentacyclic triterpenoids (**38–39**, **43–44**) and diterpenoids (**19**, **42**) have been found active against various infective strains (**Table 1** and **Figure 1**). Some of the strains studied are among the microbes listed by WHO as highly harmful and needed new drugs.

## 3. Plant-based compounds with anticancer features

The chemistry and biology of plants to fight against malignant cells are wide and diverse. Various classes of metabolites have been reported to possess valuable anticancer properties. As a recall, taxol, one of the mostly used anticancer drug in chemotherapy, is a complex diterpene-based metabolite; vinblastine, used in the therapy of various cancer as well, is made up of terpenic indol-type alkaloids and artemisinin or parthenolide actually in active clinical trials for cancer drugs possess a sesquiterpenoid lactone backbone. Since 2010, more than 72 compounds have

| Family | Species (part) | Compound name | Cancer cell lines ($IC_{50}$) | Refs. |
|---|---|---|---|---|
| Asparagaceae | *Bellevalia eigii* (bulbs) | 5,7,3′-triihydroxy-4′- methoxy Homoisoflavanone (**45**) | MDA-MB-435 (1.0 μM) | [57] |
| | | 5,3′-dihydroxy-4′,7,8-trimethoxy Homoisoflavanone (**46**) | MDA-MB-435 (1.1 μM) | |
| | | 7-*O*-methyl-3′-hydroxypunctatin (**47**) | MDA-MB-435 (4–6 μM) | |
| | *Bellevalia flexuosa* (bulbs) | 3′-hydroxy-3,9-dihydroeucomin (**48**) | MDA-MB-435 (1–6 μM); MDA-MB- 231 (9–5 μM) | [58] |
| Asparagaceae | *Urginea depressa* (whole plant) | Urgineanin A (**49**) | H522-T1 (0–071 μM); A2780 (0.32 μM); A2058 (0.068 μM) | [59] |
| | | Urgineanin B (**50**) | H522-T1 (6.78 μM); A2780 (3.4 μM) | |
| | | Urgineanin C (**51**) | H522-T1 (0.74 μM); A2780 (1.35 μM), A2058 (0.69 μM) | |
| | | Urgineanin D (**52**) | H522-T1 (0.43 μM); A2780 (0.35 μM), A2058 (0.38 μM) | |
| | | Urgineanin E (**53**) | A2780 (1.44 μM) | |
| | | Urgineanin F (**54**) | A2780 (2.3 μM) | |

| Family | Species (part) | Compound name | Cancer cell lines ($IC_{50}$) | Refs. |
|---|---|---|---|---|
| Convallariaceae | *Ophiopogon japonicus* (tubers) | Homoisopogon A **(55)** | KB (0.51 μM); LU-1 (0.66 μM); SK- Mel-2 (0.66 μM) | [60] |
| | *Ophiopogon japonicus* (roots) | 5,7,4′-Trihydroxy-3′-methoxy-6,8-dimethylhomoisoflavanone **(56)** | A549 (6.40 μM) | [61] |
| | | Methylophiopogonanone B **(57)** | A549 (0.84 μM) | |
| | | Methylophiopogonanone A **(58)** | A549 (1.66 μM) | |
| Liliaceae | *Scilla persica* (bulbs) | Scillapersicene **(59)** | AGS (8.4 μM) | [62] |
| Amaryllidaceae | *Crinum zeylanicum* (whole plant) | Ungeremine **(60)** | CCRF-CEM (4.89 μM*);* MDA-MB - *231-pcDNA* (5.47 μM); MDA-MB- 231-*BCRP* (3.67 μM); HCT116 ($p53^{+}/^{+}$) (6.45 μM) HCT116 ($p53^{-}/^{-}$) (7.06 μM); U87MG (5.38 μM) | [63] |
| Euphorbiaceae | *Macaranga balansae* (fruits) | 6,8-Diprenyl-4-methyl-naringenin **(61)** | Pan C1 (7.89 μM) | [64] |
| | | (2*S*)-6-Farnesylnaringenin **(62)** | P388 (3.27 μg/mL) | |
| | | 6-Farnesyl-3′,4′,5,7-tetrahydroxy flavanone **(63)** | P388 (2.61 μg/mL) | |
| | *Macaranga triloba* (inflorescences) | | HeLa (1.3 μg/mL), HL-60 (3.3 μg/mL) | [65] |
| Euphorbiaceae | *Macaranga tanarius* (fruits) | Vedelianin **(64)** | KB (0.050 μM), MCF-7 (0.050 μM) | [66] |
| | | Schweinfurthin E **(65)** | KB (0.050 μM), MCF-7 (0.030 μM) | |
| | | Schweinfurthin F **(66)** | KB (0.10 μM), MCF-7 (0.12 μM) | |
| | | Schweinfurthin H **(67)** | KB (0.26 μM) | |
| Thelypteridaceae | *Cyclosorus parasiticus* (leaves) | Parasiticin C **(68)** | SW1990 (2.33 μM), MDA-MB-231 (4.88 μM), MCF-7 (4.16 μM), HepG2 (1.6 μM), A.549 (5.50 μM), ALLSIL (6.06 μM) | [67] |
| | | 2′,4′-Dihydroxy-6′-methoxy-3′,5′-Dimethylchalcone **(69)** | SW1990 (6.64 μM), MDA-MB-231 (9.67 μM), MCF-7 (8.49 μM), HepG2 (2.82 μM), A549 (7.89 μM), ALLSIL (9.50 μM) | |
| Moraceae | *Artocarpus obtusus* (stem bark) | Pyranocycloartobiloxanthone A **(70)** | HL60 (0.5 μg/mL), K562 (2.0 μg/mL) | [68] |
| Guttiferae | *Calophyllum soulattri* (stem bark) | Soulattrin **(71)** | Raji (1.01 μM/mL), LS174T (1.25 μM/mL), IMR-32 (0.27 μg/mL), SK-MEL-28 (0.57 μM/mL). | [69] |
| Guttiferae | *Garcinia xanthochymus* (stem bark) | 1,3,5,6-T etrahydroxy-4,7,8-tri (3-methylbut-2-enyl) xanthone **(72)** | PC-3 (6.8 μM) | [70] |

| Family | Species (part) | Compound name | Cancer cell lines ($IC_{50}$) | Refs. |
|---|---|---|---|---|
| Papaveraceae | *Macleaya microcarpa* (roots) | Maclekarpine A **(73)** | BGC-823 (0.7 μM) | [71] |
| | | Maclekarpine C **(74)** | HCT-8 (1.9 μM), Bel-7402 (2.1 μM), A2780 (1.6 μM), A549 (3.4 μM) | |
| | | Maclekarpine D **(75)** | HCT-8 (1.9 μM), BGC-823 (0.2 μM), A2780 (2.0 μM) | |
| | | Maclekarpine E **(76)** | BGC-823 (0.1 μM) | |
| | | 6-Methoxydihydrochelerythrine **(77)** | HCT-8 (1.1 μM), Bel-7402 (0.9 μM) BGC-823 (0.8 μM), A2780 (1.8 μM) | |
| | | Dihydrosanguinarine **(78)** | HCT-8 (1.3 μM), Bel-7402 (2.3 μM) BGC-823 (0.1 μM), A2780 (2.1 μM) | |
| | | Dihydrochelerythrine **(79)** | HCT-8 (1.4 μM), BGC-823 (0.4 μM), A2780 (3.5 μM) | |
| | | 6-Butoxydihydrochelerythrine **(80)** | HCT-8 (1.7 μM), Bel-7402 (1.3 μM) BGC-823 (0.7 μM) A2780 (1.8 μM), | |
| Papaveraceae | | Bis[6-(5,6-dihydrochelerythrinyl)] ether **(81)** | HCT-8 (1.6 μM), Bel-7402 (2.1 μM) BGC-823 (0.1 μM), A2780 (1.6 μM), | |
| | | 6-Methoxydihydrosanguinarine **(82)** | HCT-8 (0.5 μM), Bel-7402 (0.5 μM) BGC-823 (0.6 μM), A2780 (0.5 μM), A549 (0.6 μM) | |
| Amaryllidaceae | *Zephyranthes candida* (whole plant) | *N*-methylhemeanthidine Chloride **(83)** | HL-60 (0.91 μM), K562 (1.0 μM), A549 (1.1 μM), HepG2 (1.5 μM), HT-29 (1.2 μM) | [72] |
| | | Hemeanthamin **(84)** | HL-60 (1.4 μM), K562 (2.5 μM), A549 (2.5 μM), HepG2 (4.8 μM), HT-29 (2.1 μM) | |
| | | Lycorine **(85)** | HL-60 (1.6 μM), K562 (2.3 μM), A549 (1.9 μM), HepG2 (3.7 μM), HT-29 (3.2 μM) | |
| | | *N*-phenethylcrinasiadine **(86)** | HL-60 (1.6 μM), K562 (2.3 μM), A549 (1.9 μM), HepG2 (3.7 μM), HT-29 (3.2 μM) | |
| Asparagaceae | *Bellevalia flexuosa* (bulbs) | Urginin B **(87)** | A2780 (0.011 μM), A2058 (0.060 μM), H522-T1 (0.044 μM) | [59] |
| | | Urginin C **(88)** | A2780 (0.041 μM), A2058 (0.076 μM), H522-T1 (0.051 μM) | |
| | | 14*β*-Bydroxy-19*β*-oxobufa-4,20, 22-trienolide-3*β*-O-*β*-D-gluco pyranoside **(89)** | A2780 (0.024 μM), A2058 (0.048 μM), H522-T1 (0.034 μM) | |
| | | 14*β*-Hydroxybufa-4,20,22-trien olide-3*β*-*O*-{α-L-rhamnopyranosyl-[(1 → 4)-*β*-D-glucopyranosyl]-(1 → 3)-*α*-L-rhamnopyranoside} **(90)** | A2780 (0.111 μM), A2058 (0.18 μM), H522-T1 (0.11 μM) | |
| Asteraceae | *Leptocarpha rivularis* | Leptocarpin **(91)** | DU-145 (2.0 μM), PC-3 (4.5 μM), HT-29 (3.8 μM), MCF7 (3.1 μM), MDA-MB-231 | [73] |

| Family | Species (part) | Compound name | Cancer cell lines ($IC_{50}$) | Refs. |
|---|---|---|---|---|
| | | | (6.4 μM), CCD 841 CoN (5.2 μM) | |
| | *Smallanthus sonchifolius (leaves)* | Enhydrin **(92)** | CCRF-CEM (3.6 μM) | [74] |
| | | Uvedalin **(93)** | CCRF-CEM (9.2 μM) | |
| | | Polymatin B **(94)** | CCRF-CEM (0.8 μM), CEM-ADR5000 (1.3 μM), MIA-PaCa-2 (3.7 μ*M*) | |
| | | Sonchifolin **(95)** | CCRF-CEM (3.1 μM), CEM-ADR5000 (3.1 μM), MIA-PaCa-2 (7.4 μ*M*) | |
| | | 8β-Angeloyloxy-9α-hydroxy-14-oxo-acanthospermolide **(96)** | CCRF-CEM (2.2 μM), CEM-ADR5000 (6.7 μM), MIA-PaCa-2 (8.9 μM) | |
| | | Fluctuanin **(97)** | CCRF-CEM (0.6 μM), CEM-ADR5000 (1.4 μM), MIA PaCa-2 (4.4 μM) | |
| | *Ambrosia cumanensis* (aerial parts) | 2,3-Dehydropsilostachyn C **(98)** | Jurkat (6.0 μM), U937 (8.0 μM) | [75] |
| | *Sonchus palustris* (roots) | 15-*p*-Hydroxyphenylacetyllactucin **(99)** | CEM (5.1 μM), BJ (9.8 μM) | [76] |
| | | 15-*p*-Methoxyphenylacetyllactucin (**100**) | CEM (3.9 μM), BJ (8.4 μM) | |
| Compositae | *Carpesium abrotanoides* (whole plant) | Caroguaianolide A (**101**) | MDA-MB-231 (7.96 μM) | [77] |
| | | Caroguaianolide B (**102**) | MDA-MB-231 (4.25 μM), HGC-2 (6.47 μM) | |
| | *Carpesium abrotanoides* (whole plant) | Caroguaianolide C (**103**) | MDA-MB-231 (2.67 μM), HGC-2 (4.83 μM) | |
| | | Akihalin (**104**) | MDA-MB-231 (4.83 μM), HGC-2 (7.35 μM) | |
| | | 4β-Hydroxy,l0β-hydroperoxyl,5αh,7αh,8βh-guaia-1,11(13)- dien-8α,12-olide (**105**) | MDA-MB-231 (5.79 μM) | |
| | | 4α-Hydroxy-1βh-guaia-9,11 **(13)**-dien-12,8α-olide (106) | MDA-MB-231 (4.07 μM), HGC-2 (8.95 μM) | |
| | | (3ar,4as,5S,7as,8S,9ar)-5-Hydroxy-4a,8-dimethyl-3-methylen-decahy droazuleno[6,5-b]furan- 2 (3H)-on (**107**) | MDA-MB-231 (5.32 μM) | |
| | *Carpesium faberi (whole plant)* | Guaianodilactones A (**108**) | CCRF-CEM (9.13 μM) | [78] |
| | | Guaianodilactones C (**109**) | CCRF-CEM (4.74 μM) | |
| | | Guaianodilactones B (**110**) | CCRF-CEM (2.03 μM) | |
| Asteraceae | *Inula japonica* (aerial part) | Neojaponicone B (**111**) | Jurkat (5.9 μM), 6 T-CEM (4.4 μM) | [79] |
| | | Inulanolide E (**112**) | Jurkat (5.5 μM), 6 T-CEM (4.6 μM) | |
| | | Inulanolide A (**113**) | Jurkat (5.8 μM), 6 T-CEM (4.3 μM) | |

| Family | Species (part) | Compound name | Cancer cell lines ($IC_{50}$) | Refs. |
|---|---|---|---|---|
| | | Japonicone Q (**114**) | Jurkat (3.3 μM), 6 T-CEM (2.7 μM) | |
| | | Japonicone N (**115**) | Jurkat (2.5 μM), 6 T-CEM (2.4 μM) | |
| | | Japonicone S (**116**) | Jurkat (4.5 μM), 6 T-CEM (3.3 μM) | |
| | | Japonicone A (**117**) | Jurkat (3.1 μM) 6 T-CEM (2.2 μM) | |

*Melanoma (MDA-MB-435, A2058 and SK-Mel-2); human non-small-cell lung (H522-T1), ovarian cancer (A2780), human epidermoid carcinoma (KB), human lung adenocarcinoma (LU-1), breast (MDA-MB-231), gastric (AGS), human myeloid leukemia (K562), human gastric (SGC-7901), human-lung-tumor (A549). Murine leukemia (P-388), human pancreatic (Pan C1 and SW1990), human cervical carcinoma (Hela), mouse leukemia (P388), human leukemia (HL-60 and ALL-SIL), mouth epidermal carcinoma cells (KB), breast cancer (MCF-7 and MDA-MB-231) lung cancer (A549), hepatocellular carcinoma (HepG2), human promyelocytic leukemia (HL60), human chronic myeloid leukemia (K562), B-lymphocyte (Raji), colon carcinoma (LS174T), human neuroblastoma (IMR-32), skin carcinoma (SK-MEL-28), colon (HCT-8), liver (Bel-7402), stomach (BGC-823), ovarian (A2780), lung (A549). Myeloid leukemia (HL-60 and K562), lung (A549), hepatocellular carcinoma (HepG2), colon (HT-29), ovarien (A2780), melanoma (A2058), non-small-cell lung cancer (H522-T1), lymphoblastic leukemia cell line (CCRF-CEM), resistant T-cell leukemia cell line (CEM-ADR5000), the pancreatic, carcinoma cell line (MIA PaCa-2)–, and on peripheral blood mononuclear cells (PBMC) from healthy human subjects, HeLa (cervical carcinoma), Jurkat (T-cell leukemia), and U937 (monocytic leukemia) cell lines, human acute lymphoblastic leukemia (CEM), and normal human skin fibroblasts (BJ), human breast (MDA-MB-231), human gastric (HGC-27), human leukemia (CCRF-CEM).*

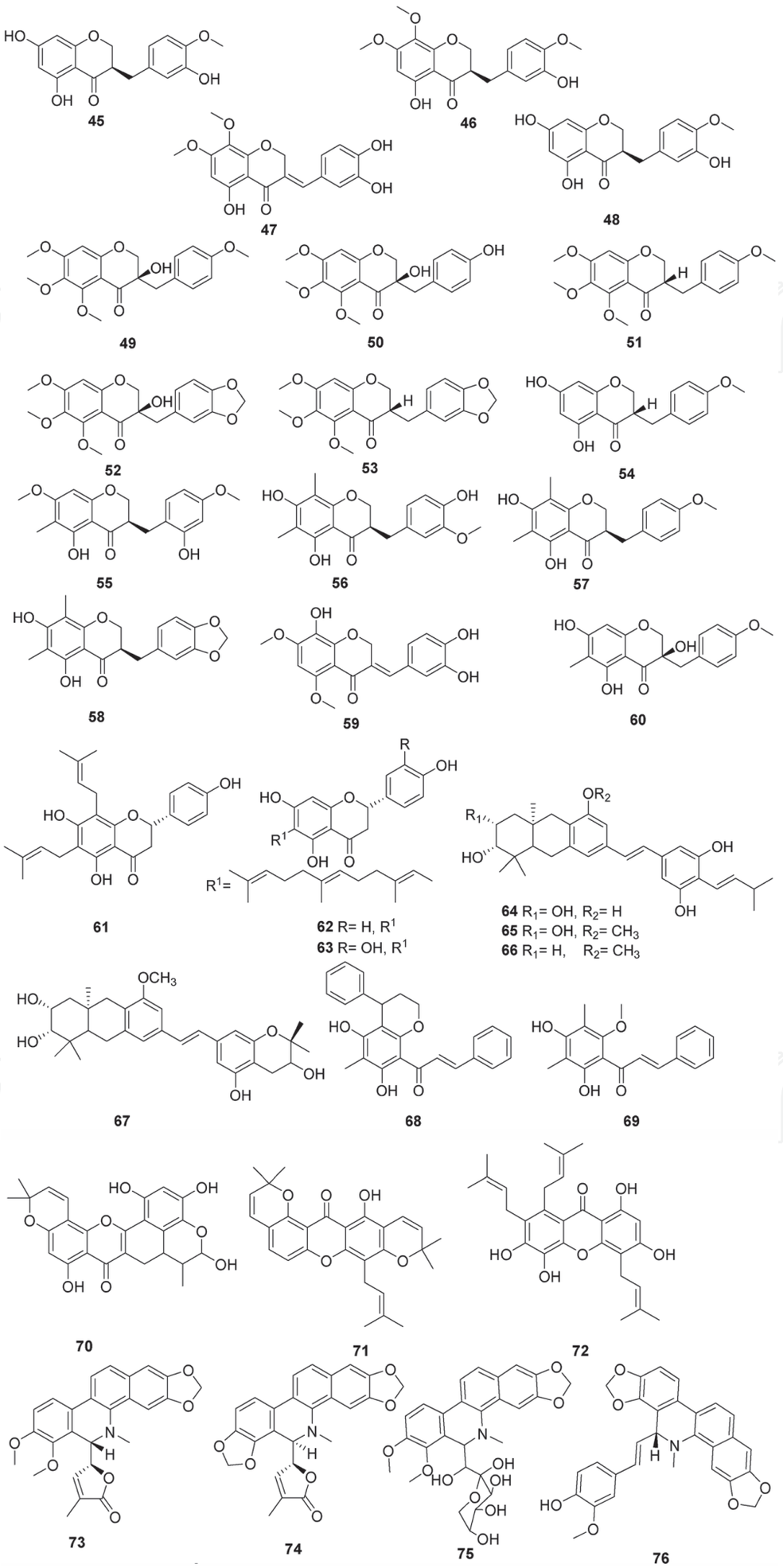
**Table 2.**
*Examples of significant secondary metabolites with antiproliferative properties.*

been reported with considerable antiproliferative activity against different cancer cell lines with $IC_{50}$ ranging from 0.001–10 μM.

These compounds are distributed in homoisoflavonoids (**45–60**), isoprenylflavonoids (**61–63**, **68–70**), stilbenoids (**64–67**), xanthones (**71–72**), benzophenanthridines (**73–82**), *Amaryllidaceae*-type alkaloids (**83–86**), cardenolides (**87–90**) and sesquiterpenoid lactones (**91–117**). Their respective sensibility toward tumor cell lines are depicted in **Table 2** and their respective structures in **Figure 2**. As expected, sesquiterpenoid lactones were the most exploited metabolites. They are reputed for their ability to induce apoptosis in cancer cell lines with good selectivity. Homoisoflavonoids were the second most important group of compounds found to exhibit high cytotoxicity herein. The interest in this class of metabolites for anticancer solution is most likely related to their potency as inhibitor of angiogenesis both *in vitro* and *in vivo*, without showing any toxicity [80]. On the other hand, benzophenanthridines are reputed for their bioavailability because they contained more often ionic bond besides their bioactivity. Their mode of action in cancer therapy includes either the inhibition of mitosis via a reaction of the imine bond with the sulfhydryl nucleophile in protein and enzyme or the enzymatic activities of DNA Topoisomerase I and Topoisomerase II by implantation into DNA molecules to retard the fast proliferation of tumor cells [81].

## 4. Natural products in active development for drug discovery

Knowing the categories of compounds which has been screened and choose for clinical trials is quite important. It can help redefine our objectives and outlines in research. However, such information is not accessible easily. Almost all pharmaceutical makers keep this information for private uses. Nevertheless, available reports before 2010 on valuable compounds in development for cancer therapy for instance can continue to be used and analyze. There are privilege structures with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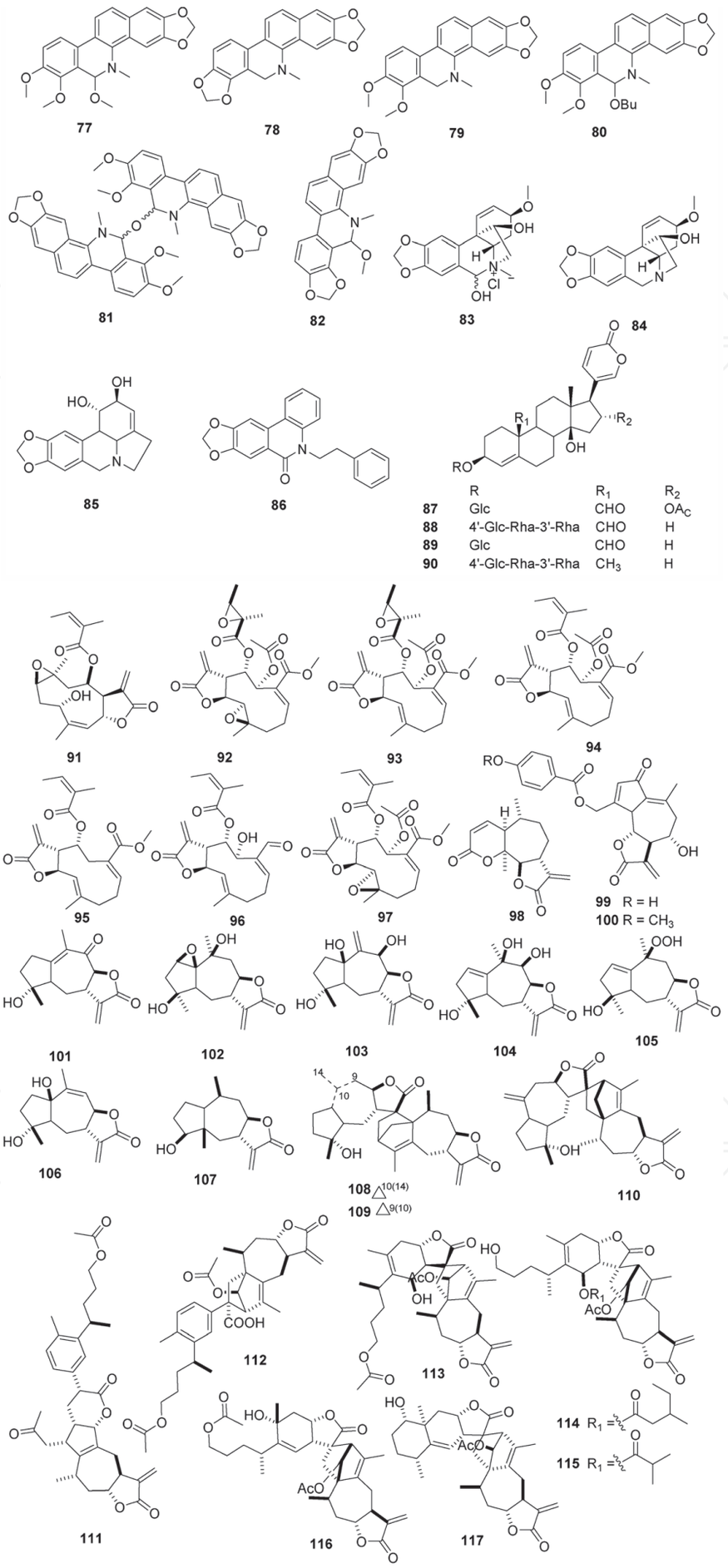


**Figure 2.**
*Bioactive compounds against cancer cell lines.*

unique structurally subunits which confer to drugs distinctive therapeutic affinities to a biological system. These core molecules include β-lactam unit like in penicillin; cyclopentanoperhydrophenanthrene fragment like in testosterone; pyrone, coumarins, isoflavone, or chalcone moieties and alkaloids like quinoline, isoquinoline or indole units.

As an example, since the large-scale screening for anticancer agents launched in the USA in 1960, more than 3000 sesquiterpene lactones have been reported. Most of them are with cytotoxic properties. Sesquiterpene lactones are well-known for their ability to bind sulfhydryl-containing peptides, mainly in proteins, presented as important route in well- programed death of a cell [82–85]. This property and other have raised up interests in this class of compounds. Many members of this class are currently in clinical trials for drug development including parthenolide, artemisinin or thapsigargin among others.

Another most important class of phytocompounds in cancer therapy is phenolic compounds. Members of these classes of metabolites are reputed in caspase activation causing apoptosis in tumor cell lines. Research found that furanocoumarins for instance in grapefruit showed significant effects towards breast cancer, the second World leading cause of cancer-related death among Women [86]. In the same line, coumarine-type of compounds known as calanolides, isolated from *Calophyllum* species have been found to be active against lymphoblastic cells infected with HIV-1 [87]. They are currently in clinical trials Phase II to drug development. Likewise, all other phenolic compounds listed above can also undergo similar interactions with cancer cells. Anthraquinones, and quinones, in general form the basic core of many anticancer drugs known as anthracyclines. Resveratrol, a stilbene-like metabolite, is being continuously checked to explain issues encountered during laboratory trials against cancer in animal model. However, association of resveratrol with established anticancer drugs like clofarabine has been proved against mesothelioma cell lines [88].

## 5. Conclusion

The World is facing an unprecedented drastic climate change that impacts negatively not only on human beings but also plants. New metabolism routes have surely emerged leading to compounds with unprecedented structures for some and with relevant bioactivities for others. However, nothing is being done to take advantages of this wealth for our health care always relying on "modern drugs." We should start exploring ways to use natural products with anticancer effects along with standard chemotherapy treatments to increase potency while reducing side effects of actual drugs. This strategy is currently being used in the USA. We highlighted relevant bio-sensibility of some compounds and they should now be investigated as main constituents to a standardization process of their respective plant extracts. The present survey can also help researchers in developing countries working on plants, to re-focus their research works.

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## Conflict of interest

The authors declare no conflict.



## Author details

Gabin Thierry M. Bitchagno[1*], Vaderament-A. Nchiozem-Ngnitedem[1,2], Nadine Tseme Wandji[3], Guy Cedric T. Noulala[3], Serge Alain T. Fobofou[4] and Bruno Ndjakou Lenta[3]

1 Department of Chemistry, University of Dschang, Dschang, Cameroon

2 Department of Chemistry, University of Nairobi, Nairobi, Kenya

3 Department of Chemistry, Higher Teacher's Training College, University of Yaounde I, Yaounde, Cameroon

4 Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, USA

*Address all correspondence to: gabin1256@gmail.com

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