Chapter 8
Plants to Drugs: A Case Study of Human Papilloma Virus and Traditional Chinese Medicine

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Abstract Various types of viral diseases are emerging as the largest menace human beings have faced in the last few decades. Since the arrival of human immunodeficiency virus, the world has seen the emergence of deadly viruses like bird flu, Ebola, Nypah, Hanta, SARS, MERS, and currently the SARS-CoV-2. Other viral diseases like herpes, human papilloma virus, and hepatitis have become so common that despite their widespread infection rates, causes of liver and cervical cancer and consequent mortalities, they have not caught the attention of the general people in a way SARS-CoV-2 has done. Unlike small pox, polio, several types of hepatitis, and, to a certain extent, HPV, most other viral diseases have proved difficult to cure with vaccines or drugs. As with many other diseases, plants can form a possible source of therapeutics for HPV. There are around 250,000 species of flowering plants in the world; each species contain a range of phytochemicals with diverse pharmacological activities. For instance, over four dozen plants have been identified with antiviral activity against herpes virus, while a number of other plants and phytochemicals have shown promise against various viruses. Promising antiviral phytochemicals include coumarins, terpenoids, flavonoids, polyphenols, and alkaloids. This chapter will attempt to summarize the present state of knowledge regarding plants, formulations, and phytochemicals (against HPV) and discuss the potential of drug discovery from the promising phytochemicals.

Keywords Human papilloma virus · Traditional chinese medicine · Phytochemicals · Cervical cancer · Anti-HPV patents

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Abbreviations

CIN	Cervical intraepithelial neoplasias/dysplasias
CIS	Carcinoma *in situ*
COVID-19	Corona virus–induced disease 2019
COX-2	Cyclooxygenase-2
DLA	Dalton's lymphoma ascites
DNA	Deoxyribonucleic acid
E6AP	E6-associated protein
HPV	Human papilloma virus
HR-HPV	High-risk HPV
HSV	Herpes simplex virus
hTERT	Human telomerase reverse transcriptase
IFN-γ	Interferon- γ
LCR	Long control region
LR-HPV	Low-risk HPV
MAP kinase	Mitogen-activated protein kinase
ORF	Open reading frame
Rb	Retinoblastoma protein
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome-corona virus-2
SJAMP	Marine japonicus polysaccharide
Sp1	Specificity protein 1
Tan IIA	Tanshinone IIT
T-bet	T-box transcription factor
Th1	T helper type 1 cells
Th2	T helper type 2 cells
TMP	Tetra-*O*-methyl nordihydroguaiaretic acid
VEGF	Vascular endothelial growth factor

1 Introduction

It has been said that interaction between viruses and humans has shaped human evolution (Leal and Zanotto 2000). Viruses like human papilloma virus (HPV) and herpes simplex virus (HSV) may have coevolved with humans since ancient times (Ong et al. 1993; McGeogh et al. 1995). In recent years, it has been reported that 219 virus species can infect humans (Woolhouse et al. 2012). In fact, viruses constitute more than two-thirds of all new pathogens that infect humans (Woolhouse and Gaunt 2007). Among the emerging viruses, zoonotic viruses play a major role in causing both human fatalities and worldwide economic disruptions. The latest virus causing the present pandemic (COVID-19) is a zoonotic virus (SARS-CoV-2), which was initially transmitted to humans from bats through a still undetermined animal species. A partial list of the more known viruses currently affecting humans is shown in Table 8.1.

Table 8.1 Selected viruses (with family) and diseases caused by them in humans

Virus family (characteristic)	Virus	Disease caused and symptoms
DNA viruses		
Adenoviridae (NE, DS linear)	Human adenoviruses A-F	Respiratory and/or ocular disease. According to American Thoracic Society, the viruses can cause a variety of illnesses such as upper and lower respiratory infections, gastrointestinal infection, neurological infection, and eye infection (Dela Cruz et al. 2019)
Hepadnaviridae (E, partial DS circular)	Hepatitis B virus (Z, possibly bat origin)	Chronic infection of liver leading to liver damage, cirrhosis, and liver cancer. Nonspecific symptoms in acute infections can be fatigue, poor appetite, nausea, vomiting, abdominal pain, low-grade fever, jaundice, and dark urine (Wilkins et al. 2010)
Herpesviridae (E, DS linear)	Human Herpes simplex virus 1	Herpetic gingivostomatitis, herpes labialis (sores around the mouth and lips, also called cold sores) (Mustafa et al. 2016)
	Human Herpes simplex virus 2	Genital herpes (clusters of inflamed papules and vesicles on the outer surface of the genitals resembling cold sores) (Mustafa et al. 2016)
	Human Herpes virus 3 or varicella-zoster virus	Chicken pox, shingles (Gebreyohannes 2014)
	Human Herpes virus 4 or Epstein Barr virus	Infectious mononucleosis, Burkitt's lymphoma, Hodgkin's lymphoma, stomach cancer, nasopharyngeal carcinoma, multiple sclerosis, and lymphomatoid granulomatosis, chronic fatigue syndrome and disorders of the immune system (Gebreyohannes 2014)
	Human Herpes virus 5 or human cytomegalovirus (CMV)	Significant morbidity, including low birth weight, hearing loss, visual impairment, microcephaly, hepatosplenomegaly, and varying degrees of mental retardation. CMV infection is strongly correlated with asymptomatic vascular diseases such as heart, coronary artery, and atherosclerosis (Gebreyohannes 2014)
	Human Herpes viruses 6, 7 and 8	Roseola infantum, pityriasis rosea, lichen planus, hypersensitivity reactions, graft-vs-host disease, and multiple other cutaneous manifestations (viruses 6 and 7); Kaposi sarcoma (virus 8) (Gebreyohannes 2014)
Papovaviridae (NE, DS circular)	Human papilloma virus (HPV)	Genital warts and warts in the throat (known as recurrent respiratory papillomatosis). Persistent infections can develop into anogenital warts, precancers, and cervical, anogenital, or oropharyngeal cancers in women and men. *The virus* can also *cause* cancers of the head and neck (Brianti et al. 2017)
Parvoviridae (NE, SS linear)	Adeno-associated viruses 1–6	Activate proto-oncogenes in human hepatocellular carcinoma (Berns et al. 2015)
	B-19 virus	The virus causes "fifth disease," a mild rash illness that affects children and occasionally adults. It can also cause severe anemia and painful or swollen joints (Heegaard and Brown 2002)

Table 8.1 (continued)

Virus family (characteristic)	Virus	Disease caused and symptoms
Poxviridae (E, DS linear)	Bovine papular stomatitis virus (Z)	Localized skin lesions. Mainly affects cattle from which it is transmitted to human beings (Temizel 2015)
	Contagious ecthyma or contagious pustular dermatitis or orf virus (Z)	Cattle disease but can cause orf in humans following transmission from cattle. Orf is characterized by small, red, itchy, or painful lump (lesion) that usually appears on the fingers, hands, forearms, or face (Taghipour et al. 2015)
	Cowpox virus (Z)	Viral skin infection in cattle, from which it can be transmitted to humans via contact with infected teats of milking cows
	Monkeypox virus (Z)	A milder form of small pox, possibly transmitted to humans by rodents and squirrels in the rain forests of Africa
	Pseudo cowpox virus (milker's nodules) (Z)	Mild infection of udders and teats in cows, from which it is commonly transmitted to ranchers, milkers, and veterinarians
	Small pox virus (variola)	Cause of small pox; a contagious, disfiguring, and often deadly disease, which has been eradicated
	Vaccinia virus (Z)	Transmitted from cattle to humans, the viral disease is characterized by focal red skin areas, fever, and general symptoms similar to those of a cold. It mostly occurs in Brazil (Silva et al. 2010)
RNA viruses		
Arenaviridae (E, SS linear segments)	Lassa virus (Z)	Causes Lassa fever, an acute viral hemorrhagic illness, transmitted through infected African mouse, *Mastomys natalensis*. Prevalent in West African countries. The virus causes multisystemic dysfunction through infecting every tissue of the body (Azeez-Akande 2016)
	Lymphocytic choriomeningitis virus (Z)	Rodent-borne viral infectious disease that appears as aseptic meningitis, encephalitis, or meningoencephalitis. Initial phase symptoms are fever, malaise, lack of appetite, muscle aches, headache, nausea, and vomiting, followed by second phase symptoms, which may consist of meningitis (fever, headache, stiff neck, etc.), encephalitis (drowsiness, confusion, sensory disturbances, and/or motor abnormalities, such as paralysis), or meningoencephalitis (inflammation of both the brain and meninges) (Bonthius 2012)
	Machupo virus (Bolivian hemorrhagic fever) (Z)	Preliminary symptoms of Bolivian hemorrhagic fever are fever, headache, fatigue, myalgia, and arthralgia. In some patients, hemorrhagic signs develop, including bleeding from nasal and oral mucosa, as well as the bronchopulmonary, gastrointestinal, and genitourinary tracts. *Calomys callosus*, a forest rodent, is the primary host of the virus (Kilgore et al. 1997)
Astroviridae (NE, SS linear)	Human astroviruses 1–8	Major cause of diarrhea in the young and the elderly. Recently, the virus has been linked to encephalitis and meningitis (Johnson et al. 2017)

Table 8.1 (continued)

Virus family (characteristic)	Virus	Disease caused and symptoms
Bunyaviridae (E, SS linear segments)	Cache valley virus	Can cause an illness with fever and in more severe cases encephalitis or meningitis. Transmitted by mosquitoes to human from infected sheep (Waddell et al. 2019)
	California encephalitis virus (Z)	Belongs to the California encephalitis virus group, which includes California encephalitis virus, La Crosse virus, and Jamestown Canyon virus in USA and Tahyna virus in Russia. California encephalitis and La Crosse virus causes encephalitis in children; Jamestown Canyon virus affects elderly individuals. Symptoms of encephalitis in children include fever, headache, vomiting, seizures, and altered mental status. These viruses infect rabbits, squirrels, and chipmunks and are transmitted by the mosquito *Aedes triseriatus* (Newhouse et al. 1963)
	Crimean-Congo hemorrhagic fever virus (Z)	Causes severe viral hemorrhagic fever with case fatality rates up to 40%. Transmitted by ticks from livestock animals like cattle, sheep, and goats. Endemic in Africa, the Balkans, the Middle East, and Asian countries south of the 50th parallel north (Flick and Whitehouse 2006)
	Hantaviruses (several serotypes) (Z)	Viral infection can cause hemorrhagic fever with renal syndrome or pulmonary syndrome. Original host found to be infected field rodent *Apodemus agrarius* near Hantan river in South Korea. Later on, it was discovered that the common deer mouse (*Peromyscus maniculatus*) was also an agent in USA (Máttar et al. 2015)
	Jamestown Canyon virus (z)	See California encephalitis virus (above)
	La Crosse virus (Z)	See California encephalitis virus (above)
	Nairobi sheep disease virus (Z)	Tick-borne virus in sheep and goats. Can cause a mild influenza-like disease in humans
	Rift Valley fever virus (Z)	Occurs in livestock. Transmitted to humans through mosquitoes causing mild flu-like illness to severe hemorrhagic fever (Bird et al. 2009)
Calciviridae (NE, SS linear)	Hepatitis E virus (Z) genotypes 1–7	Causes inflammation of liver. Depending on genotype, it can also cause acute pancreatitis, glomerulonephritis, and severe thrombocytopenia. Zoonotic Hepatitis E virus (HEV) genotype HEV-3 has been found among pigs and wild boars in Europe, whereas zoonotic genotype HEV-4 is more common in pigs in some Asian countries (Kantala and Maunula 2018)
	Noroviruses (Norwalk and Norwalk-like viruses)	Causes vomiting, diarrhea, nausea, and stomach pain (Hardy 1999)

Table 8.1 (continued)

Virus family (characteristic)	Virus	Disease caused and symptoms
	Vesicular exanthema of swine virus (Z)	Vesicular exanthema of swine virus is clinically indistinguishable from vesicular disease caused by foot-and-mouth disease virus, and vesicular stomatitis virus. Occurs in pigs and marine animals. Occasionally isolated from humans with blisters
Coronaviridae (E, SS linear)	Human coronaviruses (colds)	Four coronaviruses, namely, HCoV-OC43, H-CoV-229E, H-CoV-NL63, and HCoV-HKU1, cause common cold in children and elderly people (Tyrrell and Bynoe 1965; Hamre and Procknow 1966; van der Hoek et al. 2004; Woo et al. 2005)
	Severe Acute Respiratory Syndrome (SARS) coronavirus (Z)	Emerged in Guangdong Province in China in November 2002. Possible mode of transmission from bats to humans was through masked palm civets (*Paguma larvata*) and the raccoon dog (*Nyctereutes procyonoides*). The major clinical features include persistent fever, chills/rigor, myalgia, malaise, dry cough, headache, dyspnea, and diarrhea (Hui 2005)
	Middle East Respiratory Syndrome (MERS) coronavirus (Z)	Emerged in Saudi Arabia and other Middle Eastern countries in 2012. Possible mode of transmission from bats to humans was through camels or goats. Causes mild to severe pneumonia often accompanied by acute respiratory distress syndrome (ARDS), renal failure, pericarditis, and disseminated intravascular coagulation (DIC) (Mortazavi et al. 2014)
	Severe Acute Respiratory Syndrome (SARS) coronavirus (SARS-CoV-2)	Emerged in Wuhan, China in late December of 2019. Possible mode of transmission is from bats to humans through a yet-to-be-identified host, pangolins being the most suspected. The initial clinical features include fever, cough, shortness of breath, and muscle ache. These can progress to ARDS and multiple organ dysfunction leading to death (Tu et al. 2020)
Filoviridae (E, SS linear)	Ebola virus (Z)	First reported in the Democratic Republic of Congo in 1976. Mode of transmission to humans seems to be from fruit bats to simians to humans. Initial features of the disease include high fever, headache, vomiting, anorexia, diarrhea, and aching muscles. Advanced stages of the virus-induced disease include unexplained bleeding in the eyes, nose, gums, and gut (Kimura et al. 2015)
	Marburg virus (Z)	The first case was reported in 1967. Initial mode of transmission was possibly from the Egyptian fruit bat (*Rousettus aegyptiacus*) to African green monkeys to humans. The disease can initially start with abrupt onset of high fever, severe headache, and severe malaise followed by severe watery diarrhea, abdominal pain with cramping, nausea, and vomiting. Many patients develop severe hemorrhagic manifestations later as the disease progresses (Asad et al. 2020)

Table 8.1 (continued)

Virus family (characteristic)	Virus	Disease caused and symptoms
Flaviviridae (E, SS linear)	Dengue virus (Z)	The virus can circulate in both human and nonhuman primates and is mosquito-transmitted, particularly the *Aedes aegypti* species. Other *Aedes* species, which can transmit, include *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes scuttelaris*. Symptoms of dengue include sudden onset of fever, headache (typically located behind the eyes), muscle and joint pain, and rashes. Nausea, vomiting, and hemorrhage occur in some patients (Singh et al. 2015)
	Hepatitis C virus (HCV)	25–30% of those infected may develop symptoms like fever, jaundice, and abdominal pain. 15–20% of people with chronic hepatitis may develop cirrhosis leading to hepatocellular carcinoma. HCV can lead to extrahepatic diseases like diabetes mellitus, cryoglobulinemia, non-Hodgkin's B cell lymphoma, membranoproliferative glomerulonephritis, lichen planus, and porphyria cutanea tarda (Millman et al. 2017)
	Japanese encephalitis virus (Z)	Japanese encephalitis virus (JEV) is related to dengue virus (DENV), West Nile virus (WNV), Zika virus (ZIKV), and tick-borne encephalitis virus (TBEV). Transmitted by mosquitoes from migrating birds like herons, egrets, and ducks, which may be asymptomatic carriers. Wild and domesticated pigs also play a role in the infection chain (Filgueira and Lannes 2019)
	Louping ill virus (Z)	Tick-borne pathogen causing illness in sheep (*Ovies aries*) and red grouse (*Lagopus lagopus scoticus*) and occasionally humans (Gilbert 2016)
	Murray valley encephalitis virus (Z)	Related to the Kunjin virus, it is found in northeastern Australia and Papua New Guinea. The major vertebrate hosts are herons and egrets, particularly the Nankeen night heron (*Nycticorax caledonicus*). Transmitted through *Aedes aegypti* mosquitoes. Clinical symptoms include febrile illness with headache, myalgia, and occasional rash. Clinical encephalitis occurs in a few cases with disease varying from fever, headache, and altered mental state to coma and severe flaccid paralysis (Mackenzie et al. 2017)
	Omsk hemorrhagic fever virus (Z)	Omsk hemorrhagic fever virus (OHFV) was first reported from Omsk oblast (province) in Russia. The virus is transmitted to humans from infected muskrats (*Ondatra zibethicus*) via ticks belonging to the species, *Dermacentor reticulatus*. The initial symptoms are chills, fever, headache, and severe muscle pain with vomiting, gastrointestinal symptoms, and bleeding problems, which may be followed by inflammation of the brain (encephalitis) (Gould and Solomon 2008)

Table 8.1 (continued)

Virus family (characteristic)	Virus	Disease caused and symptoms
	St. Louis encephalitis virus (Z)	The virus was isolated for the first time from St. Louis, Missouri, USA. *Culex* mosquitoes are vectors and birds serve as hosts. Clinical manifestations include nonspecific febrile syndrome to febrile headache, aseptic meningitis, and encephalitis (Ortiz-Martínez et al. 2017)
	Tick-borne encephalitis viruses (several subtypes) (Z)	Diseases caused by these virus subtypes range throughout Europe and the northern parts of Asiatic Russia. The principal vector is the tick, *Ixodes ricinus*, the intermediary hosts being various types of rodents and carnivores. The different subtypes differ in the development of various disease forms (febrile, meningeal, meningoencephalitic, polyencephalitic, poliomyelitic, polioradiculoneuritic) and the extent of severity of these disease forms (Donoso-Mantke et al. 2011)
	Yellow fever virus (Z)	The disease is spread by *Aedes* mosquitoes with primates as hosts and is prevalent in Africa, Central and South American countries. The viral disease symptoms include asymptomatic to severe clinical signs such as muscle pain with a prominent backache, headache, loss of appetite and nausea or vomiting, jaundice dark urine and abdominal pain, and kidney and liver failure (Mulatu and Feyisa 2018)
	Wesselsbron virus (Z)	Wesselsbron virus (WSLV) was first detected in South Africa. The virus is mosquito-transmitted and its natural hosts include camels, cattle, pigs, donkeys, and horses besides wild animals like South African zebras and wild ruminants in Chad and possibly black rats (*Rattus rattus*). The disease is essentially confined to southern African countries. In humans, the infection causes arthralgia, myalgia, and fever during a short and mild acute phase (Diagne et al. 2017)
	West Nile virus (Z)	The virus is transmitted from passerine birds (like American robin or *Turdus migratorius*) by *Culex* species of mosquitoes (*Culex pipiens*, *Culex quinquefasciatus*, and *Culex tarsalis*). Infected humans can develop fever and neuroinvasive diseases (Petersen et al. 2013)
Orthomyxoviridae (E, SS linear segments)	Influenza viruses A (Z), B (Z) and C	Aquatic birds are the main carriers of the virus A and B. Host ranges of influenza virus A are humans, swine, equine, avian, canine, and marine mammals; that of B is humans only; for C the host range includes humans, swine, and canine. 500 million people die from influenza (flu) every year. Flu symptoms include fever, dry cough, sore throat, headache, fatigue, and body ache; similar symptoms are also seen in SARS-CoV-2-induced viral disease, COVID-19. Majority of human infections are caused by Type A and B viruses (Regea 2017)

Table 8.1 (continued)

Virus family (characteristic)	Virus	Disease caused and symptoms
	Avian influenza (Z)	All avian influenza viruses are Type A influenza viruses. Their hosts range from various avian species to mammalian species like swine, ferrets, mink, felids, horses, seals, whales, civets, dogs, and humans. The highly pathogenic avian influenza (HPAI) H5N1 strain is of concern to humans worldwide for its ability to create an epidemic or a pandemic (Kelly et al. 2008)
	Swine influenza (Z)	The classical swine influenza virus is a Type A (H1N1) virus, first discovered in 1930 in swine. Swine influenza can be caused by other subtypes like H1N1, H1N2, H2N3, H3N1, and H3N2. The virus can infect humans, the clinical symptoms being aches and fever, upper respiratory symptoms, weakness, and gastrointestinal disorders (Rajesh et al. 2011)
Paramyxoviridae (E, SS linear)	Hendra virus (Z)	All four species of Australian flying foxes (*Pteropus* spp.) also known as fruit bats are the natural host. Their transmission of the virus to horses is not clear. Humans can get infected through coming in contact with body fluid of horses (Hess et al. 2011)
	Human parainfluenza viruses (HPIV) 1–4	Can infect other animals apart from humans. Causes both lower respiratory infection (LRI) and upper respiratory infection (URI) (Henrickson 2003)
	Nipah virus (Z)	*Pteropus* spp. bats are the natural hosts. Can be transmitted to humans through pigs and horses. Direct transmission has also been reported from bats to humans when humans drank raw date palm sap contaminated by bats. Initial symptoms are fever, headache, and myalgia. Features of encephalitis can develop after that, the most common symptoms being altered mental status, limb weakness, hypotonia, and segmental myoclonus (Aditi and Shariff 2019)
	Respiratory syncytial virus (RSV)	The virus is the leading cause of lower respiratory tract infections in infants (Meng et al. 2014)
Togaviridae (E, SS linear)	Chikungunya virus (CHIKV) (Z)	First reported from Tanzania in 1953. Primates can be hosts of the virus. Transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. Symptoms begin with high fever. Arthralgia and rash, which can progress to rheumatic symptoms and gastrointestinal disorders (Runowska et al. 2018)

E enveloped, *NE* nonenveloped, *DS* double stranded, *SS* single stranded, *Z* zoonotic

A total of 16 virus families (6 DNA virus families and 10 RNA virus families) comprising of 17 DNA virus species and 39 RNA virus species out of 219 species are shown in Table 8.1. The surprising thing about viral diseases is that most of them lack therapeutics in the form of vaccines or drugs. Because of space constraints of the chapter, only one virus will be discussed. We have chosen to review one DNA virus

(human papilloma virus or HPV): the basis for our selection is that unlike the widely known current COVID-19 pandemic, cervical cancer due to HPV infection is a "silent" pandemic in the sense that it is the fourth most common malignant tumor affecting women in the world with around 265,672 deaths annually according to one report (Bruni et al. 2019). Another report attributes 4.5% of new cancer cases (640.000 cases) diagnosed in the world to persistent HPV infections (de Sanjosé and Tsu 2020).

Human papilloma virus has caused 79 million infections in USA alone and 14 million more are infected every year. HPV mostly affects women of underdeveloped countries. There are more than 40 sexually transmitted types of HPV affecting the epithelial lining of the anogenital tract and other mucosal areas of the human body (Findik et al. 2019). HPV causes anogenital cancers, cervical cancers, precancerous anogenital lesions, genital warts, and even can cause head and neck cancers (de Sanjosé and Tsu 2020). However, HPV infections are curable, even cervical cancer, if detected in the early stages although allopathic drugs or other measures like surgery for treatment of HPV infections may have adverse effects.

The outline followed in the present review for HPV is that of (i) describing any traditional medicinal treatments for HPV and/or its symptoms, (ii) identifying any medicinal plants and their phytochemicals responsible for their possible antiviral activities, and (iii) discussing the drug potential of phytochemicals or crude extracts of the plant(s) as shown by actual clinical trials. From scientific literature searches, it was concluded that the focus should be on traditional chinese medicines (TCMs) for TCM only showed a high diversity of plant-based formulations and potentially more promising sources of novel anti-HPV agents.

We have based our searches in the scientific literature on PubMed, SCOPUS, and Google Scholar using the terms [ethnomedicine, viral disease, or its symptoms], [phytochemicals, botanical name of the plant], [botanical name of the plant, review], [botanical name of the plant, antiviral activity], [ethnomedicine, antiviral plants], and other combinations of the above terms.

2 Human Papilloma Virus (HPV)

Human papilloma virus (HPV)is a double-stranded closed circular DNA genome virus. The virus is enveloped by a capsid containing two proteins L1 and L2. Each capsid is composed of 72 capsomeres, and each capsomere in turn is composed of five monomeric proteins of 55Kda each, forming a pentamer (Sapp et al. 1995). The HPV genome is divided into three distinct regions: the first comprises of a long control region (LCR) responsible for the regulation of transcription of E6 and E7 viral genes; the second region is an early region (E), consisting of six ORFs: E1, E2, E4, E5, E6, and E7; and the third region is a late (L) region that encodes the L1 and L2 structural proteins (Fehrmann and Laimins 2003; Jo and Kim 2005). Besides L1 and L2, the virus contains several other proteins E1–E7 of varying functions, one of the important E proteins being E6 against which most in silico inhibitor studies have been carried out. The E6 protein is responsible for binding and degrading the tumor-suppressor protein p53, inhibiting

apoptosis, interacting with proteins responsible for innate immune response (initial response to pathogens), contributing to immune evasion and persistence of virus, and activating the expression of telomerase (and so contributing to cancer).

HPV infection is common and has been reported to be detectable at least once in the lifetime of sexually active people (Park et al. 2015). There are two types of HPVs, the high-risk HPV (HR- HPV) and low-risk HPV (LR-HPV). In most cases HPV infections disappear without any interventions; in some cases of HPV 6, 11, 12, 13, 15, 32, 34, 40, 42, 43, 44, 53, 54 (LR-HPVs), infections may cause genital warts (condylomata acuminata with itching), benign papilloma, precancerous lesions, and if allowed to progress may lead to cancer. Types 6 and 11 HPVs cause genital warts in more than 90% of the cases (Gómez et al. 2012; Menéndez et al. 2004). Genital warts are one of the most common sexually transmitted diseases in the world with an estimated 600 million individuals believed to be affected. Lesions can form on the penis, vulva, scrotum, perineum, the perianal area, cervix, urethra, anus, mouth, and also in the conjunctiva, nose, and larynx (Centers for Disease Control and Prevention 2002). HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 70 (HR-HPVs) can cause cancer of cervix, vulva, vagina, penis, anus, and oropharynx, head and neck carcinomas, and contribute to over 40% of oral cancers (Forman et al. 2012; Stanley 2010), but according to Timmons et al. (2010), they cause cancer most frequently of the uterine cervix. HPV 16, 31, 32, 34, 35, 37, 42 cause Bowenoid papillosis (Zanotti and Belinson 2002). Pathogenesis of HPV and related symptoms has been reviewed by Wang et al. (2014b).

All cervical intraepithelial dysplasias (also neoplasias or CIN) are linked with certain types of cervical HPV infection. Cervical dysplasia is when there are abnormal or precancerous cells in and around a woman's cervix, cervix being the lower part of the uterus. It is well established that invasive carcinoma of cervix is preceded by a precursive lesion that morphologically resembles adjacent invasive squamous carcinomas (when the lesion has grown and progressed to the point where it has breached, penetrated, and infiltrated adjacent structures), and which lesion is termed "carcinoma *in situ*" (CIS). CIS is preceded by a spectrum of lesions that vary in degrees of abnormality with CIN 1 (cervical intraepithelial neoplasia 1) to CIN 3 ranging from small to highest levels of abnormality.

Various allopathic procedures exist to combat the HPV infections, like antiviral drugs (cidofovir), immunoenhancers (imiquimod, interferon), cytotoxic agents (5-fluorouracil), photodynamic therapy, vaccines, and surgery. All of these treatments have adverse effects or only result in partially successful treatment. Success of surgical excision of HPV-induced lower genital tract neoplasia largely depends on secondary prevention programs; chemoradiation therapy does not result in improved prognosis in about a third of cervical cancer patients; antiviral drugs, topical agents, or photodynamic therapy is somewhat successful (50–60%) in treatment of high-grade vulvar intraepithelial neoplasia (Stem et al. 2012). But the expenses associated with these allopathic methods make traditional medicines a possibly better approach, with traditional chinese medicine (TCM) playing a major role in HPV treatment. On the other hand, TCM has the disadvantage of not being known widely throughout the world and a sort of "look-down" approach from a section of scientists and allopathic doctors as to their real or perceived toxicity.

3 Traditional Chinese Medicine (TCM) Against HPV

The findings of medical research on some TCM formulations and isolated compounds have been listed (Lin et al. 2017). Essentially, traditional Chinese formulations against HPV infections can be divided into three types: internal applications taken in oral form, external applications applied on the body surface, and a combination of internal and external applications. Not all the formulations act directly on the virus; some are immunoenhancers, some strengthen the spleen or other body organs, and some are heat-clearing and detoxifying. In other words, various TCM formulations act against both HPV (anticancer, antivirus) and its symptoms, and can be both preventive and therapeutic. A number of TCM polyherbal and monoherbal formulations with their constituents and effects are shown in Table 8.2. For the sake of clarity, Table 8.2 will also give the botanical name(s) of the herbs used in the formulations. Promising phytochemicals and formulations in the light of modern scientific studies will be discussed.

4 Plant-Based Anti-HPV Formulations

HPV can cause cancer; however, before it reaches the precancerous stage and gradually progresses to cancer, HPV can cause cervical dysplasia, which, if left untreated, progresses to precancer and then cancer. TCM has formulations for various stages of HPV-induced cervical dysplasia as well as cervical cancer. In this chapter, the TCM medications for cervical dysplasia and cancer will not be differentiated; not only they will be grouped together but TCM medications discussed or given in the chapter will cover other symptoms associated with both cervical dysplasia and cervical cancer. Despite the quite large number of TCM plant–based formulations given in Table 8.2, the list is exclusive; there are other formulations, some of which will be discussed here along with an integrated medicine approach to treat HPV (combination of TCM with modern drugs). A number of them have undergone scientific testing with encouraging results. For instance, *Pinellia* extract fraction (extract of rhizomes of *Pinellia ternata* (Thunb.) Ten. ex Breitenb. (Crow dipper in English, Ban Xia in Chinese) has been shown to downregulate HPV E6 and upregulate p53 in CaSki (epidermoid cervical cancer cell line) and HeLa (human cervical cancer) cells (Li et al. 2012). In randomized control trial, Youdujing cream and external lotion were found to be effective in clearing HR-HPV infection and reversing the cervical precancerous changes, which was attributed to downregulating the mRNA expression of hTERT (human telomerase reverse transcriptase) (Xiao et al. 2012). Tanshinone IIA (TanIIA, 1,6,6-trimethyl-8,9-dihydro-7H-naphtho[1,2-g]benzofuran-10,11-dione), found in the root of *Salvia miltiorrhiza* Bunge, has been found to inhibit oncogene expression, arrest cell cycle, induce p53, and cause apoptosis in CaSki, SiHa (human cervical tumor cell), HeLa, and C33a (HPV-negative cervical cancer cell line) cells (Munagala et al. 2015).

Table 8.2 Traditional Chinese medicine formulations for treatment of HPV infections and its various symptoms with scientific justifications of their uses (if any)[a]

Formulations for internal applications		
Name of formulation	**Botanical with (English name) and parts used**	**Relevant phytochemicals and pharmacological actions with reference(s)**
Rhizoma Atractylodis	*Atractylodes macrocephala* Koidz, Baizhu in Chinese, (Atractylodes), Rhizome	Beneficial effect on spleen function and fluid metabolism. (Lin et al. 2017). Atractylone is the main component in the plant. Other uses include benefiting vital energy, eliminating dampness, hidroschesis, and soothing fetuses Gu et al. (2019)
Cortex Phellodendri	*Phellodendron amurense* Rupr. (Amur cork tree) or *Phellodendron chinense* Schneid, (Chinese cork tree), Bark	Beneficial effect on spleen function and fluid metabolism (Lin et al. 2017). Known as Huang Bai in Chinese. Crude bark contains alkaloids, isoquinoline alkaloid, limonoids, phenolic acid, quinic acid, lignans, and flavonoid. Major alkaloids include berberine, palmatine, and jatrorrhizine. Limonoids include limonin and obakunone. Pharmacological actions include antiinflammatory, antibacterial, antiviral, antitumor, antigout, antiulcer, neuroprotective, and antiatopic dermatitis effects (Sun et al. 2019). The effect of berberine was tested on HPV16-positive cervical cancer cell line, SiHa and HPV18-positive cervical cancer cell line, HeLa. Berberine modulated the activity of the transcriptional factor activator protein-1 (AP-1), which plays a central role in HPV-mediated cervical carcinogenesis (Mahata et al. 2011) Cervical erosion (CE), or cervical ectropion, is a common condition among women who have married, and is considered to be a risk factor for cervical carcinoma. An empirical formulation consisting of six Chinese herbs viz. Cortex Phellodendri, Rhizoma Coptidis, Olibanum, Myrrha, borneol and catechu has been reported to be very effective (Zhou et al. 2012)
Semen Coicis	*Coix lacryma-jobi* L. (Job's tears), Mature kernel Known as Yi Yi Ren in Chinese	Beneficial effect on spleen function and fluid metabolism (Lin et al. 2017). Recent studies showed that active ingredients in coicis semen could be used to treat flat wart, verruca vulgaris, and infectious condyloma (Lee et al. 2011a, b). Coicis semen is also applied as an adjuvant to treat stomach, colon, and cervical cancers (Hu et al. 2009). *Coix lacryma-jobi* L. var. ma-yuen (Rom.Caill.) Stapf ex Hook. f. sprout extract has been shown to significantly inhibit cell proliferation in human cervical cancer HeLa cells by inducing cell cycle arrest and apoptotic cell death through inactivation of the PI3K/AKT pathway (Son et al. 2019). Triolein from the plant has been shown to induce cell cycle arrest in MCF-7 breast cancer cells (Hien et al. 2016)
Poria	*Wolfiporia extensa* (Peck) Ginns (China root), Whole mushroom (fungus) Synonym: *Poria cocos*	Known in Chinese as Fuling. Beneficial effect on spleen function and fluid metabolism (Lin et al. 2017). It is also used to promote urination and to calm the mind. One of the active ingredient is known as *Poria cocos* polysaccharide (PCP). Its activities include antitumor, immunomodulation, anti-inflammation, antioxidation, antiaging, antihepatitis, antidiabetes, and antihemorrhagic fever effects (Li et al. 2019)

Radix Astragali	Dried root of perennial herbs, *Astragalus membranaceus* (Fisch.) Bunge (Mongolian milkvetch) and *Astragalus mongholicus* Bunge, Dried roots	Known as Huangqi in Chinese. To enhance immunity (Lin et al. 2017). According to the Chinese Pharmacopoeia (CP Volume 1 of 2015 Edition), it possesses tonic, hepatoprotective, diuretic, and expectorant properties (Ma et al. 2002). More than 200 compounds have been isolated and identified from *Astragalus* root, including saponins, flavonoids, and polysaccharides (Liu et al. 2017). Isoflavonoids, triterpene saponins, and polysaccharides are the main bioactive compounds (Song et al. 2007). One of the constituents, formononetin, could significantly inhibit the PI3K/AKT signaling pathway to induce the apoptosis of cervical cancer HeLa cells and is considered as a potential drug (Jin et al. 2014). Besides cervical cancer, formononetin is also active against ovarian, breast, prostate, non-small cell lung, and bladder cancer (reviewed in Guo et al. 2019)
Radix Angelicae Sinensis	*Angelica sinensis* (Oliv.) Diels (Winter cherry root), Dried root	Known as Danggui in China. Used in TCM to enrich blood, promote blood circulation, treat blood deficiency pattern and menstrual disorders such as dysmenorrhea and irregular menstrual cycle, and modulate the immune system. Contains phthalides (both monomeric and dimeric) (Lin et al. 2017; Wu and Hsieh 2011). The herb has been in use in China for thousands of years for treatment of women's reproductive disorders. Ethanol extract of roots, when tested on human breast (MCF-7 and 7368) and cervical (CaSki and SiHa) cancer cells, killed over 90% of cancer cells at a dose of 0.32 μg/ml (Zhu et al. 2012)
Flos Lonicerae	*Lonicera japonica* Thunb. (Japanese honeysuckle), Flower More known as Lonicerae japonicae flos	Known as Shan Yin Hua in Chinese. Chinese Pharmacopoeia (2005) distinguishes between Lonicerae flos (all other species of *Lonicera*) and Lonicerae japonica flos (*Lonicera japonica*), although they have similar efficacies. Heat-clearing and detoxifying herb, which is capable of relieving genital itching and pain. Extracts and its active components including chlorogenic acid, flavonoid, caffeoylquinic acid, and iridoid glycoside can inhibit herpes simplex keratitis, influenza virus pneumonia, influenza A virus, porcine reproductive and respiratory syndrome virus, Newcastle disease virus, respiratory syncytial virus, influenza virus, human cytomegalovirus, Coxsackie *β*3 virus, and enteric cytopathic human orphan 19 virus (Lin et al. 2017; Li et al. 2015)
Herba Hedyotis Diffusae	*Hedyotis diffusa* Willd. (Snake needle grass), Whole plant Known as Bai Hua She She Cao in Chinese	Heat-clearing and detoxifying herb, which is capable of relieving genital itching and pain. For thousands of years, has been used in TCM for inflammation-linked diseases such as urethritis, appendicitis, and hepatitis. Recent scientific studies have shown the herb's efficacy against colorectal cancer, leukemia, liver cancer, lung cancer, breast cancer, cervical tumor, prostate cancer, and multiple myeloma (reviewed by Chen and others) (Lin et al. 2017; Chen et al. 2016). Contains the iridoid compounds asperuloside, geniposidic acid, diffusoside A and B; triterpenes – arborinone, isoarborinol, oleanolic and ursolic acids; flavonoids – amentoflavone, quercetin, rutin, kaempferol; various anthraquinones; and phenolic acids including ferulic and caffeic acids (Chen et al. 2016). Amentoflavone has been shown to induce apoptosis in human cervical cancer cells via suppressing HPV E7 expression (Lee et al. 2011a, b). Also see below

Herba Scutellariae Barbatae	*Scutellaria barbata* D. Don (Chinese skullcap), Whole plant	Known as Ban Zhi Lian in Chinese, Heat-clearing and detoxifying herb, which is capable of relieving genital itching and pain. Over hundreds of years, the whole herb has been in use in TCM for treating symptoms associated with carbuncle, scrofula, hematemesis, epistaxis, ascites, traumatic injuries, and especially tumors (mainly lung, breast, and digestive system cancers). The plant contains scutellarin, which is active against breast cancer cells, hepatoma, and colon cancer cells. Diterpenoid alkaloids of the plant, Scutebarbatines A-L, X, are active against nasopharyngeal cancer, oral epidermoid carcinoma, lung cancer, colorectal carcinoma, colon cancer, prostate cancer, melanoma, breast cancer, gastric cancer, leukemia, and hepatoma cancer (Lin et al. 2017; Gao et al. 2019)
Herba Lobeliae Chinensis	*Lobelia chinensis* Lour. (Chinese Lobelia herb), Whole plant Known in Chinese as Ban Bian Lian	Heat-clearing and detoxifying herb, which is capable of relieving genital itching and pain. The main constituents of the plant include piperidine alkaloids and flavonoids. Anticancer effects are shown by the piperidine alkaloids, namely, norlobelanine, lobeline, lobelanidine, lobelanine, radicamine A, and radicamine B. A decoction of the herb can restrain growth of liver cancer and the alkaloids can inhibit growth of BC-38 gastric cancer cells. Constituent flavonoids like apigenin and luteolin can promote apoptosis in colorectal cancer cell line, COLO205, as well as HCT 116 and HeLa cells of cervical cancer. A review of the anticancer effects of luteolin reported the compound to be effective against cancer cells of breast, colon, pancreatic, prostate, oral, lung, kidney, cervical, placental, ovarian, skin, liver, gastric, esophageal, and bladder cancers as well as glioblastoma. Apigenin reportedly inhibited proliferation in human head and neck and oral squamous cancer cells, induced apoptosis in anaplastic thyroid carcinoma cells, blocked progression of progestin-dependent BT-474 breast cancer cell, suppressed proliferation of several colorectal adenocarcinoma cell lines, and was effective against skin, liver, and pancreatic cancer cells (Lin et al. 2017; Chen et al. 2014; Imran et al. 2019; Madunić et al. 2018)

Modified Simiao Decoction*, main components containing Radix Astragali 20 g, Rhizoma Atractylodis 15 g, Cortex Phellodendri 15 g, Semen Coicis 30 g, Radix Angelicae Sinensis 15 g, Poria 15 g, Faeces Trogopterpri 10 g, Flos Lonicerae 15 g, Herba Hedyotidis Diffusae 30 g, Herba Scutellariae Barbatae 10 g, Herba Lobeliae Chinensis 10 g, Radix Glycyrrhizae 10 g *Simiao means temple in Chinese. However, in this case the name comes from Sun Simiao, author of the earliest Chinese Encyclopedia for Clinical Practice (circa 652 AD) [http://www.itmonline.org/arts/sunsimiao.htm]	Radix Astragali: see above. Rhizoma Atractylodis: see above Cortex Phellodendri: see above Semen Coicis: see above Radix Angelicae Sinensis: see above Poria: see above Flos Lonicerae: see above Herba Hedyotidis Diffusae: see above Herba Scutellariae Barbatae: see above Herba Lobeliae Chinensis: see above Radix Glycyrrhizae: Root of *Glycyrrhiza glabra* L. (licorice) Faeces Trogopterpri: Feces of flying squirrel (*Trogopterus xanthipes*)	The decoction reportedly exhibited better improvement of clinical symptoms compared with the classic Chinese medicine formulation Baofukang in patients with cervical HPV infection. Clearance of virus was greater and there was higher level of interferon-α (IFN-α) and tumor necrosis factor-α (TNF-α), those being positive signs of antiviral and immune-regulatory effects (Dou et al. 2013; Cheng et al. 2015) *Glycyrrhiza glabra* roots have been reported to contain the triterpenoid saponins glycyrrhizin, 18β-glycyrrhizic acid and other triterpenes including liquiritic acid, glycyrretol, glabrolide, isoglaborlide, and liquorice acid. Flavonoids and chalcones isolated from *Glycyrrhiza glabra* included flavonoids like liquiritin, liquiritigenin, hamnoliquiritin, and neoliquiritin; chalcones included isoliquiritin, isoliquiritigenin, neoisoliquiritin, licuraside, glabrolide, licoflavonol, 5,8-dihydroxy-flavone-7-*O*-β-D-glucuronide, glychionide A, and 5-hydroxy-8-methoxyl-flavone-7-*O*-β-D-glucuronide and glychionide B. Reported isoflavones included glabridin, galbrene, glabrone, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin, kumatakenin, hispaglabridin A, hispaglabridin B, 4′-*O*-methylglabridin, 3′-hydroxy-4′-*O*- methylglabridin, glabroisoflavanone A and B. *Glycyrrhiza glabra* extracts and glycyrrhizic acid have been reported to inhibit the replication of several viruses included Epstein-Barr virus, Herpes simplex virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Human cytomegalovirus, Human immunodeficiency virus, Influenza virus, SARS coronavirus, and Varicella zoster virus. Root methanolic extract had a growth inhibitory action against intestinal carcinoma cell line Caco-2 and prostate carcinoma cell line PC-3 with IC_{50} values of 40 and 40.6 μg/ml, respectively. Isoliquiritigenin, present in the root, prevented the incidence of 1,2-dimethylhydrazine-induced colon and lung tumors in mice (reviewed by Al-Snafi 2018a). Glycyrrhizinic acid along with a food supplement has been found to be effective for treatment of HPV-induced anogenital warts (Gómez et al. 2012). The roots of *Glycyrrhiza uralensis* are also used in TCM against recurrent respiratory papillomatosis (Yarnell 2015) A total of 54 fecal medicines are used in traditional Chinese formulations; the common ones are Wu-Ling-Zhi, Jiu-Fen and Hei-Bing-Pian. Most fecal medicines are used to treat gastrointestinal, nervous system, skin, and gynecological diseases (Du et al. 2019).

Yiqi Huashi Jiedu Decoction, composed of Radix Astragali 15 g, Poria 20 g, Rhizoma Atractylodis Macrocephalae 15 g, Cortex Phellodendri 10 g, Rhizoma Cyrtomii 10 g, Fructus Amomi 10 g, Radix Angelicae Sinensis 10 g, Rhizoma Chuanxiong 10 g, Radix Gentianae 6 g, Radix Glycyrrhizae 6 g Added Fructus Toosendan and Rhizoma Corydalis for patients with abdominal pain; Cortex Magnoliae Officinalis for poor appetite; and Semen Euryales for leukorrhagia	Radix Astragali: see above Poria: see above Rhizoma Atractylodis Macrocephalae: see above Cortex Phellodendri: see above Rhizoma Cyrtomii: Rhizome with leafstalk of *Dryopteris crassirhizoma* Nakai (thick stemmed wood fern) Fructus Amomi: Mature fruit of *Amomum villosum* Lour. (Cocklebur-like Amomum) Radix Angelicae Sinensis: see above Rhizoma Chuanxiong: *Rhizome* of *Ligusticum chuanxiong* Hort. (Sichuan lovage) Radix Gentianae: Root of *Gentiana lutea* L. (Gentian root) Radix Glycyrrhizae: see above Fructus Toosendan: Fruit of *Melia toosendan* Siebold & Zucc. (Toosendan fruit) Rhizoma Corydalis: Rhizome of *Corydalis tuberosa* DC. (Hollowroot) Cortex Magnoliae Officinalis: The dried bark or bark of branch or root of *Magnolia officinalis* Rehd. (Magnolia) Semen Euryales: Seed of *Euryale ferox* Salisb. (Gordon Euryale)	This decoction is another classic formulation that is believed to have the power of activating blood circulation, dissipating blood stasis, eliminating necrotic tissues, promoting granulation, dissipate heat, and enhancing diuresis (Lin et al. 2017). According to He et al. (2015), Yiqi Huashi Jiedu Decoction showed higher clinical healing rate, better virus clearance, and less recurrence than routine western medical treatment in patients with HPV infection and cervicitis (Lin et al. 2017; He et al. 2015) Rhizome extract of *Dryopteris crassirhizoma* reportedly inhibited all four serotypes of dengue virus (Maryam et al. 2020). Bornyl acetate is the main constituent in *Amomum villosum* fruit; it reportedly showed analgesic and anti-inflammatory activity in rodents (Wu et al. 2005) Essential oil in rhizomes of *Ligusticum chuanxiong contains ligustilide, cnidilid, neocnidilide, senkyunolid, butylidenephthalide, sabinene, α-firpene, and myrcene; rhizomes contain the alkaloids chuanxiongzine and pelolyfine as well as phenolic compounds like ferulic and sedanonic acids, and other compounds like spathulenol and apigenin, quercetin and cosmosiin* (Ran et al. 2011). *A Chinese herbal medicine containing Ligusticum chuanxiong has been shown to* block cancer transformation of experimental oral precancerous lesion (Chen et al. 2004) *Gentiana lutea* is also an Ayurvedic plant, used for its immunostimulatory properties and contains bitter phytoconstituents like amarogentin, gentiopicrinor, gentiopicroside, gentiolutelin and its dimethyl acetal, gentioluteol, gentanine, amaroswerin, gentioside, and gentiolutelin (Prakash et al. 2017). The plant can be used against chemotherapy-induced mucositis (Meyer-Hamme et al. 2013) Fruits of *Melia toosendan* contain limonoids including 12-O-methyl-1-O-deacetylnimbolinin B, 12-*O*-methy-1-*O*-tigloyl-1-*O*-deacetylnimbolinin B, 12-*O*-ethylnimbolinin B, and 1-*O*-cinnamoyl-1-*O*-debenzoylohchinal and tirucallane-type triterpenoids, named meliasenins S and T (Hu et al. 2011). Significant cytotoxic activity against KB* cells has been reported for limonoids (meliatoxin B1 and toosendanin) from the plant (Tada et al. 1999). [*KB is now known to be a subline of the ubiquitous KERATIN-forming tumor cell line HeLa. KB cells have been reported to contain human papillomavirus18 (HPV-18) sequences.] *Corydalis tuberosa* is known to contain the isoquinoline type alkaloid thalictricavine (Manske 1953). The quinoline/isoquinoline nucleus can play a major role in the development of anticancer drugs (Diaz et al. 2015) *Magnolia officinalis* bark contains two major polyphenolic neolignans, magnolol and honokiol (Amblard et al. 2007; Kong et al. 2005). The two compounds are active against multiple human cancer cell lines including HeLa (human cervix adenocarcinoma cell line) and RKO (human rectal carcinoma cell line); for a complete review, see Poivre and Duez (2017). Other compounds found in the bark essential oil include bornyl acetate, camphene, caryophyllene epoxide, α-, β- and γ-eudesmol, cryptomeridol, α- and β-pinene; bark constituents further include bornyl-magnoliol, caddeic acid, quercetin, and kaempferol; alkaloids present in the bark include anonaine, liriodenine, and magnocurarine *Euryale ferox* seeds are also used in Ayurveda for uterine weakness; the main bioactive component has been reported to be valerianic acid (Sidh and Sharma 2019). Other constituents isolated from ethanol extract of seeds include protocatechuic acid, gallic acid, gallic acid ethyl ester, 5,7-dihydroxychromone, β-sitosterol, daucosterol, and 5,7-dihydroxy-6,4′-dimethoxyflavone (Sun et al. 2014). Seeds also contain 2β-hydroxybetulinic acid 3β-caprylate, which reportedly has antidiabetic and hepatoprotective potential (Ahmed et al. 2015)

(continued)

Formulations for external applications		
Name of formulation	**Botanical with (English name) and parts used**	**Action(s) with Reference(s)**
Baofukang Suppository. Main contents are Rhizoma Curcumae and Borneolum	Rhizoma Curcumae is rhizome of *Curcuma longa* L. (turmeric) Borneolum is the processed item from resin of *Dryobalanops aromatica* Gaertn. f. (Borneo camphor in English)	*One study* (Shen et al. 2013) *found that a 3-month medication of Baofukang reduced human papilloma virus (HPV) by 38%. Comparison of Baofukang with INF-α2b (interferon-α2b) showed that Baofukang had a better HPV negative rate and higher cervical intraepithelial neoplasia I (CIN I) reversal rate. Curcumin, present in rhizomes of Curcuma longa, has been shown in several studies to have anti-HPV effects, which has been reviewed by* Mishra and Das (2015). *A patent (CN103041283A) has been granted for a Chinese medicine composition to treat cervical HPV infection, which contains borneolum. Patent No. CN103041283A, granted 2014-10-22* Essential oil of exudates from *Dryobalanops aromatic* reportedly contained terpenoid compounds like borneol, α- and β-caryophyllene, α-pinene, α-terpineol, and terpinen-4-ol (Le et al. 2016)
Radix Sophorae Flavescentis	Root of *Sophora flavescens* Ait. (Ku Shen in Chinese, yellow sophora in English)	A polyherbal formulation named YIKEER containing root of *Sophora flavescens* is used to treat verruca (warts). Bioactive components include matrine, an alkaloid present in *Sophora flavescens,* which reportedly demonstrated antitumor effects against liver, breast, pancreatic, myeloma, and gastric cancer cell lines. (Jiang et al. 2019). Other flavonoids such as kuraninone and sophoraflavonone are also thought to be biologically active and may have antiviral effects. [https://www.mskcc.org/cancer-care/integrative-medicine/herbs/sophora-flavescens]
Zhimiling suppository (ZMLS) intravaginal suppository, ingredients including Cortex Phellodendri, Radix Sophorae Flavescentis, Catechu, and Borneolum	Catechu (betel nut)	An empirical formulation consisting of six Chinese herbs viz. Cortex Phellodendri, Rhizoma Coptidis, Olibanum, Myrrha, borneol, and catechu has also been reported to be very effective against cervical erosion associated with chronic cervicitis. Note that this formulation contains three ingredients of ZMLS It is also interesting that both formulations contain catechu. Catechu is regarded as one of the most potent substances associated with oral carcinoma by HPV-16 and HPV-18: both are also causative agents for cervical carcinoma (Zhou et al. 2012; Chakraborty et al. 2014)

Paiteling, composed of Herba Hedyotis Diffusae, Folium Isatidis, Fructus Cnidii, and Fructus Bruceae	Herba Hedyotis Diffusae is the whole plant of *Hedyotis diffusa* Willd. (see above) Folium isatidis is the leaf of *Isatis indigotica* Fort. (known as Da Qing Ye in Chinese and Dyers Woad Leaf in English Fructus Cnidii is the fruit of *Cnidium monnieri* (L.) Cusson (known in English as Cnidium and in Chinese as She chuang zi) Fructus Bruceae is the fruit of *Brucea javanica* (L.) Merr. (known in Chinese as Ya Dan Zi and in English as Java Brucea)	*Hedyotis diffusa* (Bai Hua She She Cao or BHSSC) has been shown to induce murine and human antigen-presenting cell (APC) activation via the MAPK signaling pathway and enhance antigen presentation in bone marrow–derived dendritic cells (BMDCs) *in vitro*. Variant peptide-based vaccines combined with BHSSC were shown to improve antitumor activity in preventive, therapeutic, and recurrent HPV-related tumor models. Rutin was found to be the active constituent, which induced a strong specific immune response against HPV-related tumors *in vivo* (Song et al. 2020) Extract of Folium Isatidis has been found to be active against influenza A virus (IAV), coxsackie virus B3 (CVB3), respiratory syncytial virus (RSV), and adenovirus type 7 (Ad-7) (Deng et al. 2013). Application of Paiteling to vaginal stump accelerated the positive to negative conversion of high-risk HPV (HR-HPV) after hysterectomy for cervical intraepithelial neoplasia (CIN) (Zhao et al. 2018) Coumarins may play a role in the activity of Cnidium fruits in alleviating HPV symptoms or inhibiting the virus itself. Some of the coumarins present are xanthotoxin, isopimpinellin, bergapten, imperatorin, and osthole, which are present in crude extract used for treatment of pain in female genitalia. Bergapten possesses anticancer, analgesic, and anti-inflammatory activities (Qian et al. 2007). Imperatorin showed strong cytotoxic activity on human leukemia, and chemopreventive effects on hepatitis and skin tumor (Li and Chen 2004) Various quassinoid group of compounds (some with anticancer activity) are the main constituents of *Brucea javanica* (Zhao et al. 2014)
Zibai gel, the active ingredients being Radix Arnebiae, Rhizoma Curcumae, Cortex Phellodendri, Flos Lonicerae, and Radix Sophorae Flavescentis	Radix Arnebiae (Arnebia Root or Gromwell Root in English, Zi Cao in Chinese) is the dried root of Arnebia euchroma (Royle) Johnst. or Lithospermum erythrorhizon Sieb. et Zucc. or Arnebia gutfata Bunge (Family Boraginaceae)	The gel has been found to reduce HPV load, effectively relieve symptoms, and improve cytological and pathological results for cervical infected patients (Ma et al. 2012). Any scientific reports on Radix Arnebiae and HPV have not been reported thus far. Certain polyphenols inhibit the proliferation of HPV cells; it has been reported that in a clinical trial, a daily oral dose of 0.5–12 g curcumin (present in Rhizoma Curcumae) resulted in histologic improvement of precancerous lesions in one out of four patients with uterine cervical intraepithelial neoplasms (Moga et al. 2016) According to TCM, *Arnebia* root is useful in cardiovascular and skin diseases (Ma et al. 2014). *Arnebia* species are rich in naphthoquinones such as alkannins, shikonins, and their derivatives, which may have antitumor activity (Hosseini et al. 2018)
Youdujing cream containing Fructus Bruceae, Rhizoma Curcumae, and Radix Arnebiae	For more about the ingredients, see above	The cream has been reported to be clinically effective against cervical infected patients and also used against condyloma acuminatum (anogenital warts caused by HPV). *In vitro* experiments with the cream showed inhibition of HPV-DNA amplification (Xiao et al. 2011; Hou et al. 1998; Feng et al. 2004)
Formulations for both internal and external applications		
Name of formulation	**Botanical with (English name) and parts used**	**Action(s) with Reference(s)**

(continued)

Combination of Folium Isatidis, Radix Isatidis, and Herba Portulacae	Radix isatidis is the dried roots of the plant *Isatis indigotica* Fort. or *Isatis tinctoria* L. (Fam. Brassicaceae). Known in Chinese as Ban Lan Gen and in English as woad dyer's woad or glastum. Folium isatidis is the leaf blade of the same plant Herba Portulacae is *Portulaca oleracea* L. (known in Chinese as Ma Chi Xian and in English as purslane)	In traditional chinese medicine, pathogenic heat and toxins (inflammatory factors) are causes of cancer and can promote its virulence (Zhang et al. 2017). The combination of Folium Isatidis, Radix Isatidis, and Herba Portulacae is thought to be good for cancer cure through eliminating pathogenic heat and toxins. Herba Portulacae and Radix Isatidis are among the two most used herbs to treat HPV. Clemastanin B, 7*S*,8*R*,8'*R*-(−)-lariciresinol-4,4′-bis-*O*-β-D-glucopyranoside, a lignan isolated from roots of *Isatis indigotica*, has been found to be active against different subtypes of human (H1N1, including swine-origin H1N1; H3N2 and influenza B) and avian influenza viruses (H6N2, H7N3, H9N2) (Yang et al. 2013). Bioactive flavonoids of *Portulaca oleracea* include kaempferol, myricetin, luteolin, apigenin, quercetin, genistein, and genistin (Zhu et al. 2010)

Decoction containing Poria 30 g, Rhizoma Dioscoreae Hypoglaucae 15 g, Radix Achyranthis Bidentatae 12 g, Semen Coicis 30 g, Radix Stephaniae Tetrandrae 10 g, Fructus Forsythiae 12 g, Radix Angelicae Dahuricae 10 g, Rhizoma Atractylodis Macrocephalae 10 g, Herba Violae 15 g, Cortex Phellodendri 12 g, Radix Glycyrrhizae 6 g, with Herba Hedyotidis Diffusae, Herba Patriniae, and Herba Portulacae for patients with excessive heat and toxin; Flos Carthami and Semen Persicae for genital drying; Fructus Kochiae and Cortex Dictamni for genital itching.	Rhizoma Dioscoreae Hypoglaucae is the *rhizome* of perennial herbaceous plant *Dioscorea septemloba* Thunb. It is known in Chinese as Bei Xie and in English as fish poison yam Radix Achyranthis Bidentatae is the dried roots of *Achyranthes bidentata* Bl. It is known in Chinese as Niu Xi and ox knee in English Radix Stephaniae Tetrandrae is the root of *Stephania tetrandra* S. Moore. Known in Chinese as Han Fang Ji and Fourstamen Stephania in English Fructus Forsythiae is the dried fruit of *Forsythia suspensa* (Thunb.) Vahl. It is known in English as Weeping forsythia and in Chinese as Lian Qiao Radix Angelicae Dahuricae is the root of *Angelica dahurica* (Fischer ex Hoffmann) Bentham & J. D. Hooker ex Franchet & Savatier, Enum. Known in Chinese as Bai Zhi and in English as Chinese Angelica Herba Violae (*Viola tricolor* L.), Chinese name Zi Hua Di Ding, English name Wild Pansy Herba Patriniae is the entire plant of *Patrinia scabiosaefolia* Fisch. ex Trev. Known in English as Patrinia herb and in Chinese as Bai Jiang Cao	The decoction exhibited significant improvement of cervicitis combined with intravaginal Baofukang suppository (Qin et al. 2016) Cholestane glycosides, dioseptemlosides A and B, together with six spirostane glycosides, dioseptemlosides C-H, were isolated from the rhizomes of *D. septemloba*. Other compounds isolated from the rhizomes include diaryl-heptanoids, dioscorol A, dioscorosides E1, E2; two new stilbenes, dioscorosides F1 and F2; 1,7-bis(4-hydroxyphenyl)-hepta-4*E*,6*E*-dien-3-one, 1,7-bis(4-hydroxy-phenyl)-1,4,6-heptatrien-3-one, 3,5-dihy-droxy-1,7-bis(4-hydroxyphenyl)heptane, (3*R*,5*R*)-3,5-dihydroxy-1,7-bis(4-hydroxy-phenyl)heptane 3-*O*-β-D-glucopyranoside, (3*R*,5*R*)-3,5-dihydroxy-1,7-bis(4-hydroxy- 3-methoxyphenyl)-heptane 3-*O*-β-D-gluco-pyranoside, and 3-*O*-[α-L-arabinopyrano-syl(1→6)-β-D-glucopyranosyl]oct-1-ene-3-ol (Salehi et al. 2019) Stigmasterol, stigmasteryl glucoside, *β*-sitosteryl glucoside, betaine hydrate, betaine hydrochloride, succinic acid, oxalic acid, *γ*-aminobutyric acid, *α*-spinalsterol, *β*-sitosterol, chrysophanol, dibutyl phthalate, palmitic acid, and daucosterol have been reported from *A. bidentata*. Two new isoflavonoid glucosides, achyranthosides A and B, were separated from the roots of *A. bidentata* (reviewed by Yang et al. 2019). It is to be noted that another plant belonging to the same genus, *Achyranthes aspera*, is used in Ayurveda for removing warts; intralesional infiltration of Apamarga Ksharodaka (AK), i.e., aqueous solution of Apamarga (*Achyranthes aspera*) Kshara (alkaline ash of the herb) took 2–6 days for the warts to shed off (Gundeti et al. 2014) *Stephania tetrandra* roots contain monobenzyltetrahydroisoquinoline alkaloids like N-methylcoclaurine, juziphine, coclaurine, protosinomenine, reticuline, and oblongine among others; BISBENZYLTETRAHYDROISOQUINOLINE alkaloids – tetrandrine, fangchinoline, oxo-fangchirine, cycleanorine, cycleanine, homoaromaline, stephibaberine, cepharanthine, and obaberine among others; aporphine alkaloids like dicentrine, tazopsine, isoboldine, and corytuberine among others; and protoberberine and tetrahydroprotoberberine alkaloids (reviewed in Jiang et al. 2020). A number of the first three group of alkaloids have reported antitumour and anticancer activities (Jiang et al. 2020) A total of three hundred and twenty-one compounds were identified from Forsythiae Fructus, including fifty-one phenylethanoid glycosides, fifty lignans, nineteen aliphatic alcohols with the C6-C2 skeleton, two iridoids, nineteen diterpenoids, twenty-seven triterpenoids, six sterols, nineteen flavonoids, fifty-two volatiles, seven alkaloids, twenty-eight organic acids, six amino acids, nine sugar derivatives, two allylbenzene glycosides, and twenty-four others. Some flavonoids are rutin, quercetin, isorhamnetin, kaempferol, hyperin, baicalin, and hesperidin (Dong et al. 2017) Angelicae dahuricae radix is a traditional herbal medicine used to treat various diseases in China and Korea, such as colds, headaches, rhinitis, and psoriasis (Jeong et al. 2015). Imperatorin, a fumarocoumarin isolated from the roots, was found to inhibit the human liver cancer cell line HepG2 through induction of apoptosis by both death receptor– and mitochondria-mediated pathways (Luo et al. 2011). Other coumarins in the root INCLUDE isoimperatorin, bergapten, oxypeucedanin, byakangelicin, oxypeucedanin hydrate, and cnidilin (Yang et al. 2020). Roots of a related species *Angelica sinensis* (Oliv.) Diels, Dong Quai in Chinese, are used in TCM for treatment of recurrent respiratory papillomatosis (Yarnell 2015) *Viola tricolor* contains 0.3% of salicylic acid and its derivatives such as the methyl ester and violutoside (the glucosidoarabinoside of salicylic acid methyl ester); phenol carboxylic acids such as *trans*-caffeic acid, protocatechuic acid, *p*-coumaric acid; flavonoids (rutin, violaquercitrin, violanthin, scoparin, saponaretin, orientin, vicenin, and anthocyanidin glycosides); carotenoids (violaxanthin, zeaxanthin); and coumarins: umbelliferone (Rimkienė et al. 2003). The herb has been reported to be used after surgery to prevent reoccurring tumors (McGuffin et al. 1997). Various solvent fractions, especially ethyl acetate fraction, showed activity against MCF-7 human breast cancer cells and inhibited angiogenesis in chicken chorioallantoic membrane (Sadeghnia et al. 2014)

(continued)

	Flos Carthami is dried floret of *Carthamus tinctorius* L. (safflower in English and Da Hong Hua in Chinese) Semen Persicae is the dry ripe seed of deciduous tree *Prunus persica* (L.) Batsch or *Prunus davidiana* (Carr.) Franch. (known as peach seed in English and Tao Ren in Chinese) Fructus Kochiae is the desiccative ripe fruit from *Kochia scoparia* (L.) Schrad. It is known as Di Fu Zi in Chinese and broom cypress in English Cortex Dictamni is the dried root bark of *Dictamnus dasycarpus* Turcz Chinese name is Bai Xian Pi, English name is dittany	Two species, *Patrinia scabiosaefolia* Fisch. ex Trev. and *Patrinia villosa* Juss., are considered as Herba Patriniae in TCM. Various classes of compounds are present in Herba Patriniae, including triterpenoid aglycones and triterpenoid saponins (scabiosides, patrinovilosides), flavonoids (acacetin, luteolin, apigenin, scutellarin, quercetin, kaempferol, catharcitin), organic acids, iridoids, and volatiles. Anticancer effects of Herba Patriniae have been shown in CRC cell line SW480, SMMC-7721, A375-S2, A549, HeLa; HepG2, HT1080, K562, HL-60 and U937 cells, AGS, SGC-7901, BV-2, 5-FU/HCT-8, HepG2, HT-29, HeLa and MDA-MB-231cells, A498, A549, BEL-7402, HT-29, MCF-7, K562, SGC-7901, and various other cell lines (reviewed in Gong et al. 2020) Flos Carthami, the dried floret of *Carthamus tinctorius* L. (safflower in English and Da Hong Hua in Chinese), is used in TCM to treat coronary heart disease, anginapectoris, gynecologic disease, stroke, and hypertension (Tu et al. 2015). According to Zhang et al. (2016), flavonoids and alkaloids, especially the quinochalcone c-glycoside hydroxysafflor yellow A, *N*-(*p*-Coumaroyl)serotonin, and *N*-feruloylserotonin, are responsible for most of the pharmacological activities of the plant. Flower extract has been found to relieve inflammation and retard progression of skin tumors (Hiramatsu et al. 2009) Semen Persicae can promote blood circulation and dissipate stasis (Lin et al. 2017). Phytochemicals present include neochlorogenic acid, chlorogenic acid, rutin, and cyaniding-3-rutinoside (Lara et al. 2020). It has been shown that curcumin and rutin can downregulate cyclooxygenase-2 (COX-2) and reduce tumor-associated inflammation in HPV-16 transgenic mice (Moutinho et al. 2018) Various formulations containing Cortex Dictamni have been found useful for atopic dermatitis and other skin diseases (Yan et al. 2020). Anti-inflammatory limonoid compounds have been isolated from Cortex dictamni, namely, dictamlimonol A, dictamlimonoside B, and dictamlimonols C-F. as well as limonin, limonin diosphenol, obacunon, 7α-obacunyl acetate, fraxinellone, 9β-hydroxyfraxinellone, and dasylactone A; fraxinellone is the main anti-inflammatory compound in the root bark (Chen et al. 2020) Fructus Kochiae total flavonoids have been shown to give an anti-inflammatory effect through activation of the pERK1/2/TLR4/NF-κB pathway (Xiao et al. 2018). [ERK = Extracellular signal–regulated kinase; TLR4 = toll-like receptor 4, its activation leads to activation of NF-κB or nuclear factor-kappa B, which in turn is responsible for activating the innate immune system]. While the Chinese use it for the treatment of diseases of the skin, urinary tract, and eyes, in Korean traditional medicine, it is used as tonic, diuretic, analgesic, and antidote and for the treatment of cutaneous pruritus and thermal skin diseases, and in China, Japan, and Korea, Fructus Kochiae is used to treat dysuria, skin diseases, and cancers (Al-Snafi 2018b). Triterpenoid glycosides isolated from the fruits of *Kochia scoparia* include momordin Ic, the 6′-methyl ester of momordin Ic, its 2'-*O*-β-D-glucopyranoside, momordin IIc, scoparianosides A, B, and C, 2'-*O*-β-D-glucopyranosyl momordin Ic, 2'-*O*-β-d-glucopyranosyl momordin IIc, momordin lb., its 6'-*O*-methyl ester, and oleanolic acid; flavone glycosides isolated from Fructus Kochiae include quercetin3-*O*-β-d-apiofuranosyl-[1 → 2]-β-d-galactopyranosyl-7-*O*-β-d-glucopyranoside, quercetin 3-*O*-α-l-rhamnopyranosyl-[1 → 6]-β-d-galactopyranosyl-7-*O*-β-d-sophoroside, quercetin 7-*O*-β-d-gluco pyranoside, quercetin 3-*O*-β-d-apiofuranosyl-[1 → 2]-β-d-galactopyranoside, quercetin 3-*O*-β-d-galactopyranosyl-7-O-β-d-glucopyranoside, and quercetin 7-*O*-β-d-sophoroside (reviewed by Al-Snafi 2018b). The anti-inflammatory and analgesic effects of methanol, ethanol, and aqueous extracts of dried fruits have been shown experimentally (Kim et al. 2016; Shin et al. 2004; Choi et al. 2014). Methanol extract of Fructus Kochiae inhibited human breast cancer cell MDA-MB-231 and oral squamous cell carcinoma (OSCC). Momordicin Ic induced HepG2 cell apoptosis (Han et al. 2014, 2016); Wang et al. 2014a)

1 [a]The main point to be noted is that not all TCM formulations for treatment of HPV and its symptoms have been given in Table 8.2. Traditional Chinese medicine has more formulations for HPV and associated symptoms; to discuss them is beyond the scope of this chapter. Another main point to be noted is that in Column 2 of Table 8.2, English and botanical names of plants and plant parts are provided to facilitate understanding. Also to be noted is that the English names of a number of TCM formulations are not available, so the Chinese names have been given in English, as they are quoted in the English scientific literature

Dehydrocostus lactone, a natural sesquiterpene lactone, can be obtained from *Saussurea lappa* Clarke (Lin et al. 2015). The compound can inhibit cell proliferation, inhibit invasion, and induce apoptosis in HeLa and C33a (human cervical cancer cell line) cells (Jiang et al. 2015). Butein is a chalcone (2′,3,4,4′-tetrahydroxychalcone), which can be found in *Toxicodendron vernicifluum* (Stokes) F A Barkley and *Butea monosperma* (Lam.) Taubert. Reported activities of this compound include reduced cell viability, increased apoptosis, and DNA damage in MCF-7 (Michigan Cancer Foundation-7, a breast cancer cell line), HeLa, and ME180 (human cervical carcinoma cell line) cells (Tong et al. 2016). Erhuang powder is composed of Daihuang and Huangqi (Guo et al. 2016). The root or rhizome of perennial herbaceous plant *Rheum palmatum* L., or *Rheum tanguticum* Maxim. ex. Balf. or *Rheum officinale* Baill is called Da Huang or Daihuang; Radix Astragali is also known as Huangqi or Huang Qi. In vaginal lavage and cervical tissue of HPV-infected CIN I patients, Erhuang powder regulates Th1/Th2 [helper T cells expressing cytokines, Th1 expresses the proinflammatory cytokine interferon-γ (IFN-γ), while Th2 expresses interleukins 4, 5, and 13 and interleukin 10, an anti-inflammatory cytokine] balance and increases IFN-γ and T-bet (T-box transcription factor, also called TBX21, facilitates IFN-γ expression) (Xu and Yuan 2016).

Yi Gan Kang, a TCM formulation of which three of the major constituents are whole plant of *Angelica sinensis* (Oliv.) Diels (Apiaceae/Umbelliferae family), *Radix Astragali* (roots of *Astragalus mongholicus* Bge. (Leguminosae family), and whole plant of *Salvia miltiorrhiza* Bge. (Labiatae family), has been shown to benefit the liver and used for treatment of liver fibrosis (Yao et al. 2005). It was discovered that the medication downregulated E6 and E7 oncogenes while upregulating p53 and p21 expression in the HeLa cervical cancer line, thus proving its efficacy in HPV treatment (Deng et al. 2006).

5 Marine-Based Anti-HPV Formulations

Nonplant items used for liver ailments have been found to remove lumps and warts (Lin et al. 2017); an example is Concha Margaritifera (Zhen Zhu Mu or mother-of-pearl shell), which in TCM is used to pacify liver [https://tcmwiki.com/wiki/zhen-zhu-mu]. Concha Ostreae (Mu-li in Pinyin Chinese) can be the shell of any or all three species of oyster [*Crassostrea gigas* Thunberg (*Ostrea gigas* Thunberg), *Crassostrea talienwhanensis* Crosse, and *Crassostrea rivularis* Gould]; among other uses, its TCM uses include tinnitus, scrofula, subcutaneous nodules (Yang et al. 2012). Concha Ostreae has also been reported to remove lumps and warts (Lin et al. 2017).

Wang et al. (2014b) have listed several anti-HPV compounds from marine organisms. From red algae, they have listed γ-, κ-, and τ-carragenan and agar; from brown algae, alginic acid, and fucoidan; and from marine fungus, gliotoxin, neoechinulin A, physcion, and (+)-epoxydon. Marine japonicus polysaccharide (SJAMP) isolated from *Stichopus japonicus* Selenca could significantly inhibit the proliferation of human cervical carcinoma HeLa cell *in vitro* (Niu and Song 2010).

6 Integrative Treatment for HPV-Induced Conditions

Integrated treatment can consist of one TCM herbal formulation with another TCM herbal formulation, combination of two different methods of treatment (both within TCM like acupuncture/moxibustion/Tai Chi with herbal formulation), or a TCM formulation/method with a Western drug or surgery. Acupuncture has been used in combination with TCM herbal treatment for HPV infections. A 32-year-old woman was treated for myoma for 2 years prior to treatment for HPV. Myoma treatment consisted of 10 acupuncture treatments, *Cordyceps synensis* (Berk.) Sacc. (a mushroom type known as caterpillar fungus in English and Dong Chong Xia Cao in Chinese) tea capsules 1.5 g per day and Yunnan Baiyao tea capsules 1 g per day in a period of 4 months. HPV treatment was done with 10 acupuncture treatments and 1.5 g *Cordyceps synensis* tea capsules per day in a period of 3 months. Following treatment, clinical examinations did not show any signs of myoma or HPV (Jihe et al. 2020). The mushroom contains cordycepin (Liu et al. 2015), a compound, which has reportedly shown anticancer activities against B16 mouse melanoma and Lewis lung carcinoma (LLC) cells (Nakamura et al. 2015). The exact composition of Yunnan Baiyao is a closely guarded secret; however, some details are provided in Table 8.3.

A combination of Ezhuyou- N-CWS [*Nocardia rubra* cell wall skeleton (N-CWS) having antitumor and adjuvant activities; *Nocardia* is a genus of weakly staining Gram-positive, catalase-positive, rod-shaped bacteria] and Chinese medicine Ezhuyou (having antimicrobial activities) inhibited *in vitro* proliferation of HeLa cells and gave beneficial results in patients with cervical HPV infection (Chi and Li 2009). Ezhuyou or Ezhu You contains oil obtained from rhizomes of *Curcuma zedoaria* Rosc.; the main ingredients of the herb include curzerene, eucalyptol, curcumol, pyridine, germacrone, β-elemene, τ-elemene, and 28 other ingredients, including curdione; the oil was found to inhibit proliferation of AGS (human gastric adenocarcinoma hyperdiploid cell line) cells (Shi et al. 2013); curdione, which is also present in *Curcuma aromatica* Salisb., besides *Curcuma zedoaria*, plays an

Table 8.3 Composition of Yunnan Baiyao TCM formulation

Proprietary Blend	总成分	500 mg
Radix Notoginseng (root of *Panax notoginseng* (Burk.)[a]	田七	200 mg
Ajuga Forrestii Diels (*Ajuga forrestii* Diels plant)	散瘀草	85 mg
Rhizoma Dioscoreae (dried rhizome of *Dioscorea opposita* Thunb.)	淮山药	66.5 mg
Rhizoma Dioscoreae Nipponicae (dried rhizome of *Dioscorea nipponica* Makino)	穿山龙	57.5 mg
Herba Geranii & Herba Erodii[b]	老鹤草	36 mg
Dioscoreae Parviflora Ting (*Dioscorea parviflora* C T Ting)	苦良姜	30 mg
Herba Inulae Cappae (*Inula cappa* (Buch.-Ham. ex D.Don) DC	白牛胆	25 mg

Source: https://www.activeherb.com/baiyao/

[a]A bioactive constituent of steamed ginseng showed cytotoxicity in HeLa and MS751 human cervical cancer cell lines (Liang et al. 2015)

[b]Herba Geranii and Herba Erodii are *Geranium thunbergii* Siebold et Zuccarini and *Erodium stephanianum* Willd., respectively

important role in the inhibitory effect of the plant on cytochrome P450 3A4 (CYP3A4) in Caco-2 (human epithelial colorectal adenocarcinoma) cells (Hou et al. 2011). Isocurcumenol, another compound present in rhizomes of *Curcuma zedoaria*, showed concentration- and time-dependent increase in the percentage of cytotoxicity in Dalton's Lymphoma Ascites (DLA), adenocarcinomic human alveolar basal epithelial cells (A549), myelogenous leukemia cell line (K-562), and KB cells (subline of HeLa cells) (Lakshmi et al. 2011). Thus, although the anti-HPV component in essential oil remains to be identified, it is possible that the compound may have the potential of becoming a therapeutic against HPV.

Surprisingly, despite the widespread prevalence of HPV, allopathic anti-HPV drugs have not been discovered so far. The Food and Drug Administration of USA approved the use of Antiviral 2 (AV2®, Cesa Alliance, Luxembourg) containing the phytochemicals carvone, eugenol, geraniol, and nerolidol; these compounds together have a broad spectrum of antiviral activities. Preliminary clinical studies have shown that the drug is quite efficacious against cervical lesions but did not show 100% efficacy (reviewed by Mutombo et al. 2017). It would be interesting to see clinical trials of AV2 along with a TCM anti-HPV formulation to determine whether full efficacy for HPV treatment can be achieved.

7 Phytochemicals as Anti-HPV Drugs

Unlike viruses of other diseases (sexually transmitted or not), human papillomaviruses lack specific targets for the drug to act, the result being that HPV therapy consists of antimitotics or immunomodulators (Mlynarczyk-Bonikowska et al. 2013). In the absence of synthetic antiviral drugs, initial attention has focused on plant secondary metabolites like podophyllotoxin, and catechins like epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate, the action of the catechins is to inhibit HPV E6 and E7 protein expressions (Mlynarczyk-Bonikowska et al. 2013). On the other hand, as shown in Table 8.2, a large number of phytochemicals can possibly be new sources of anti-HPV therapeutics. It has to be clarified at this point that while TCM considers even crude powdered plant(s) as "drugs," in Western terminology, the paradigm of "one drug one therapy" means that a single compound should be considered as a drug even though many "drugs" may be used to combat the main disease and its associated symptoms. However, from TCM anti-HPV medications, a number of bioactive compounds appear to be promising anti-HPV candidates.

Berberine, formononetin, chlorogenic acid, amentoflavone, quercetin, rutin, kaempferol, scutellarin, apigenin, luteolin, glycyrrhizic acid, spathulenol, honokiol, genistein, baicalin, hesperidin, bergapten, and imperatorin can be possible candidates for HPV therapy, to name only a few. At the very least, some of the phytochemicals can act as therapeutics for HPV symptoms or boost the immune system, if not against the virus itself. The flavonoid quercetin has been reported to induce G2 phase arrest and apoptosis with the activation of p53 in HPV-positive human

cervical cancer–derived cells (Clemente-Soto et al. 2019). Another flavonoid compound, hesperidin (present in citrus species), reportedly induced apoptosis in MSTO-211H (established in 1985 from the pleural effusion of a patient with biphasic mesothelioma of the lung) cells by inhibiting specificity protein 1 (Sp1) transcription factor (Lee et al. 2012). Though hesperidin is yet to be reported for any activity against HPV, another flavonoid found in citrus species plants, naringin, is known to inhibit growth and induce apoptosis in HeLa cervical cancer cells (Zeng et al. 2014). Luteolin has been shown to disrupt binding between HPV16 E6 and E6AP (E6-associated protein) and so decrease viability and proliferation of HPV-positive cells (Cherry et al. 2013).

Besides flavonoids, α-linoleic acid, which is found in a number of TCM formulations presented in Table 8.2, can regulate Cox2/VEGF/MAP kinase pathway and decrease the expression of HPV oncoproteins E6/E7 through restoration of p53 and Rb expression in human cervical cancer cell lines (Deshpande et al. 2016). Limonoid group of compounds obtained from *Azadirachta indica* A. Juss. has been reported to be effective against gynecological cancers, including cervical cancers (Moga et al. 2018). Lignans have also been found to be effective against HPV. TMP or tetra-*O*-methyl nordihydroguaiaretic acid, originally found in the resin of the creosote bush, was made into a vaginal ointment and, when applied to women with HPV-linked cervical intraepithelial neoplasia, showed an excellent safety profile in Phase I/II trials (Khanna et al. 2007). The existing scientific reports suggest that quite a number of phytochemicals may prove to be of value in the treatment of HPV and/or its symptoms but at the moment lack adequate experiments done on them followed by proceeding for clinical trials (see Table 8.2 for more phytochemicals relevant for HPV treatment or prevention). The structures of some phytochemicals relevant to HPV treatment are given in Fig. 8.1.

8 Patents for Anti-HPV Formulations or Drugs

A number of patents have been granted in China for treatment of HPV and its symptoms, some of which are presented in this chapter. A patent has been granted in China in 2014 for 75% ethanol extract of *Euphorbia ebracteolata* Hayata, which purportedly contains "*Euphorbia ebracteolata* Hayata first element, *Euphorbia ebracteolata* Hayata second element, the plain A of *Euphorbia ebracteolata* Hayata, *Euphorbia ebracteolata* Hayata element B, 24-methylene cycloartanol, *Euphorbia ebracteolata* Hayata element C, β-Amyrin acetas, triterpenic acid, euphorbin A, 3-acetyl-α-Amyrin, rock Radix Euphorbiae Pekinensis lactone B, ebractelatinoside B, ebractelatinoside C, isoquercitrin, Radix Euphorbiae Fischerianae (Radix Euphorbiae Ebracteolatae) first element, Radix Euphorbiae Fischerianae (Radix Euphorbiae Ebracteolatae) second element, and 2-hydroxyl-6-methoxyl group-3-methyl acetophenone 2–4-beta-glucosidase" for treating human papillomavirus infection symptom. The patent CN102335223B was filed on 2010-07-29 and granted on 2014-01-01 [https://patents.google.com/patent/CN102335223B/en].

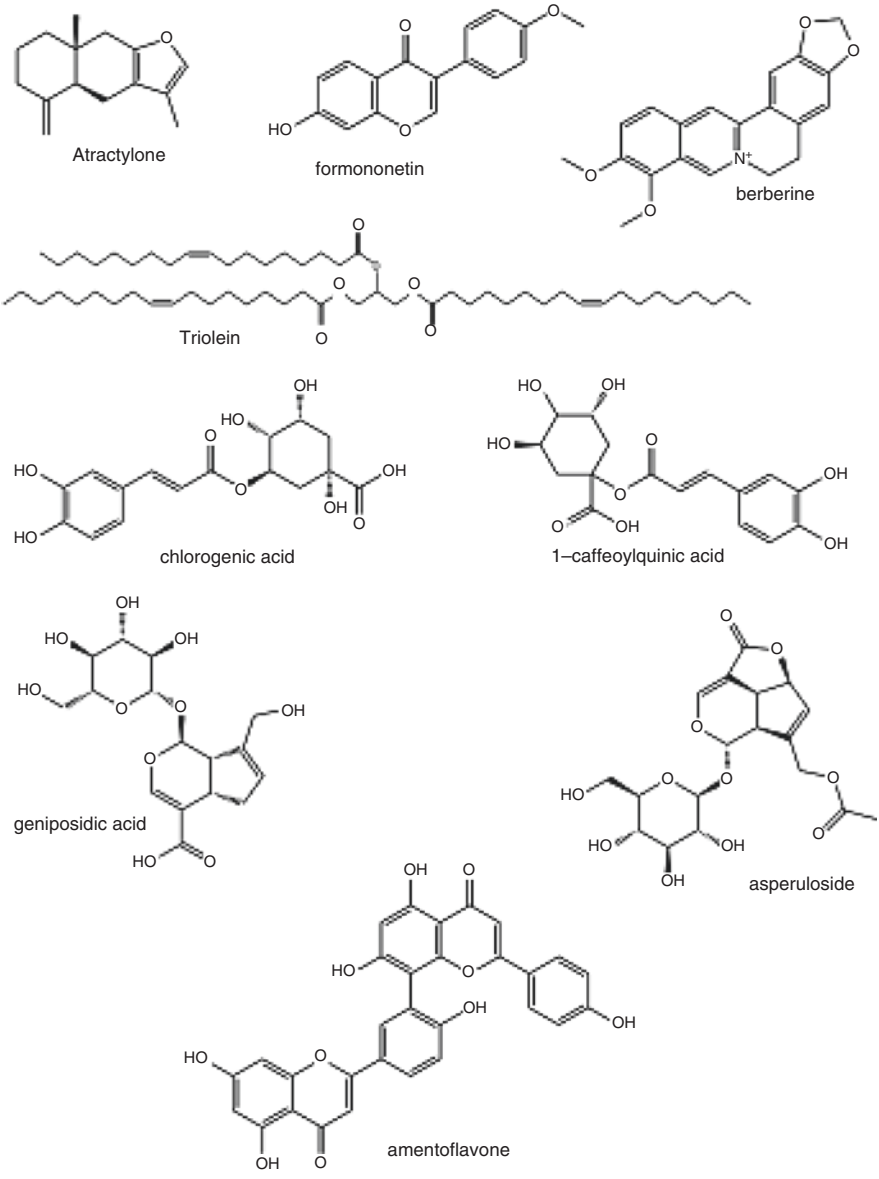

Fig. 8.1 Structure of selective phytochemicals with potential therapeutic significance against HPV and its symptoms

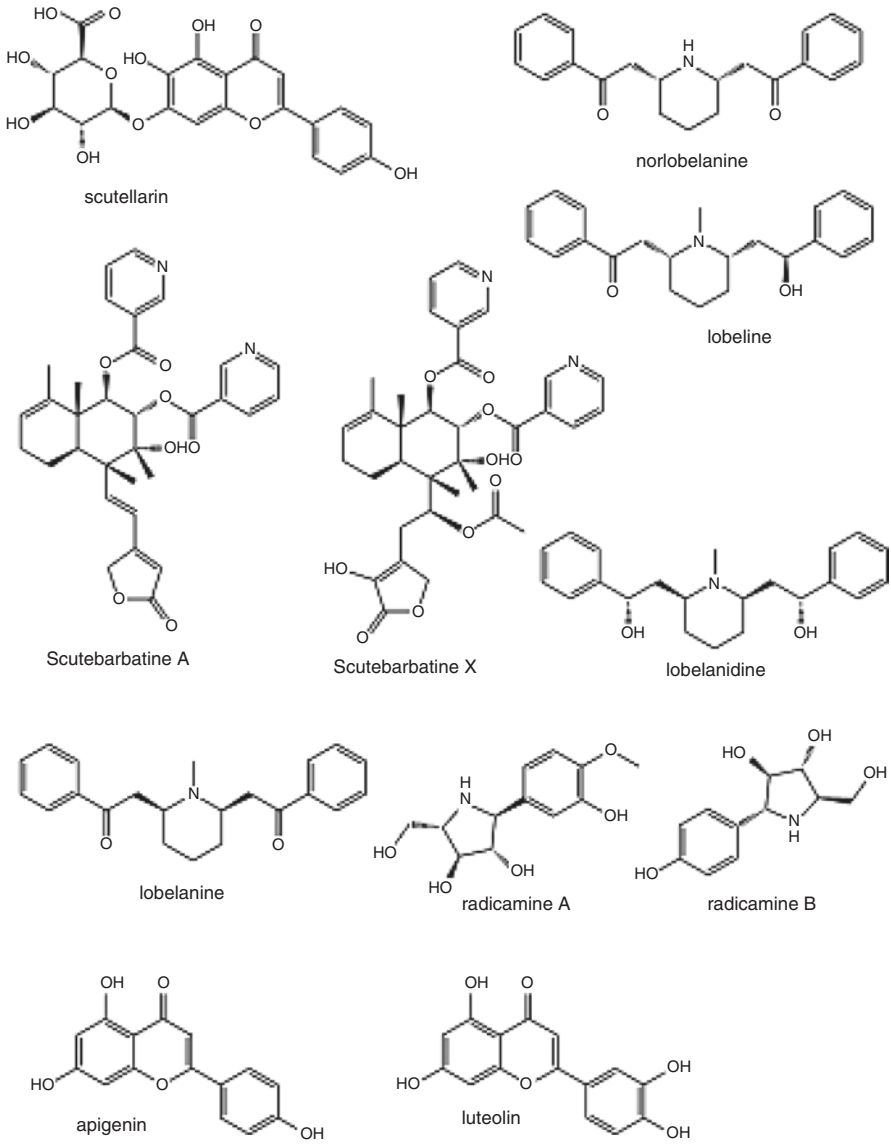

Fig. 8.1 (continued)

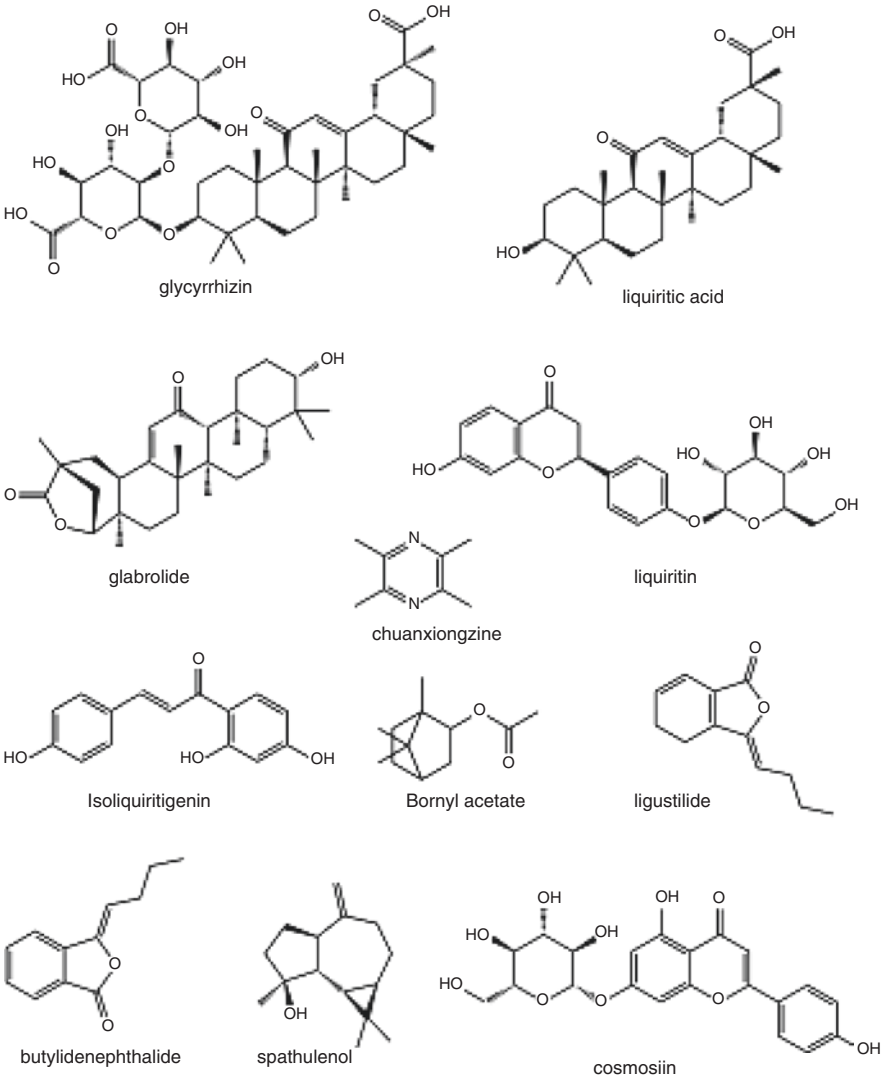

Fig. 8.1 (continued)

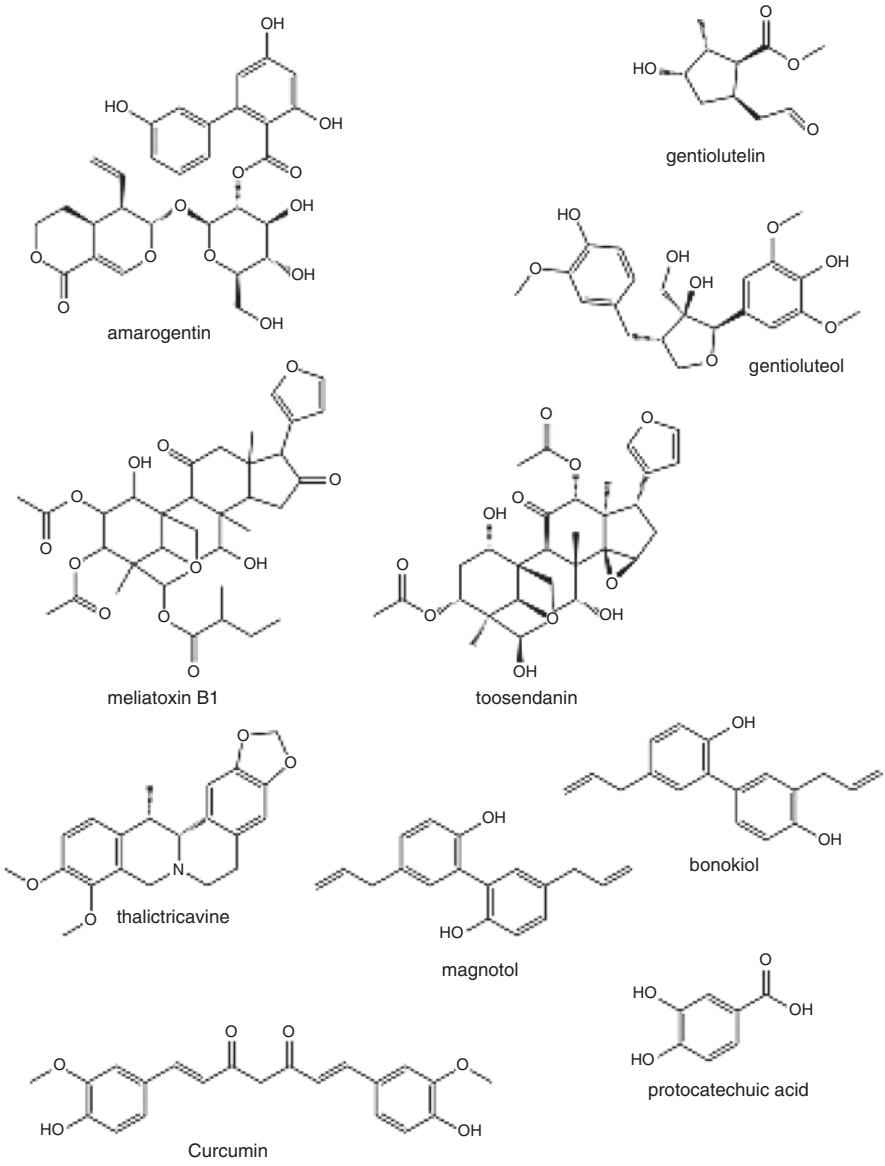

Fig. 8.1 (continued)

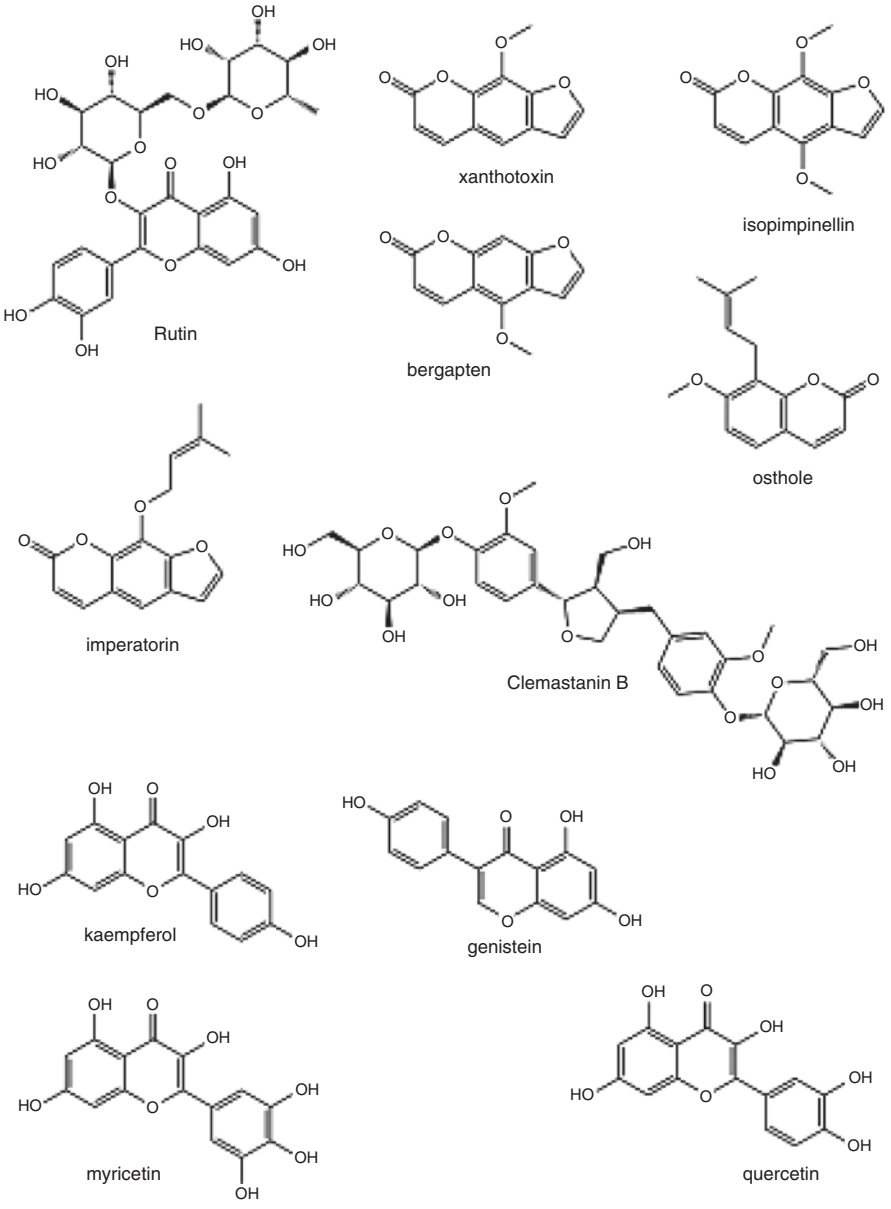

Fig. 8.1 (continued)

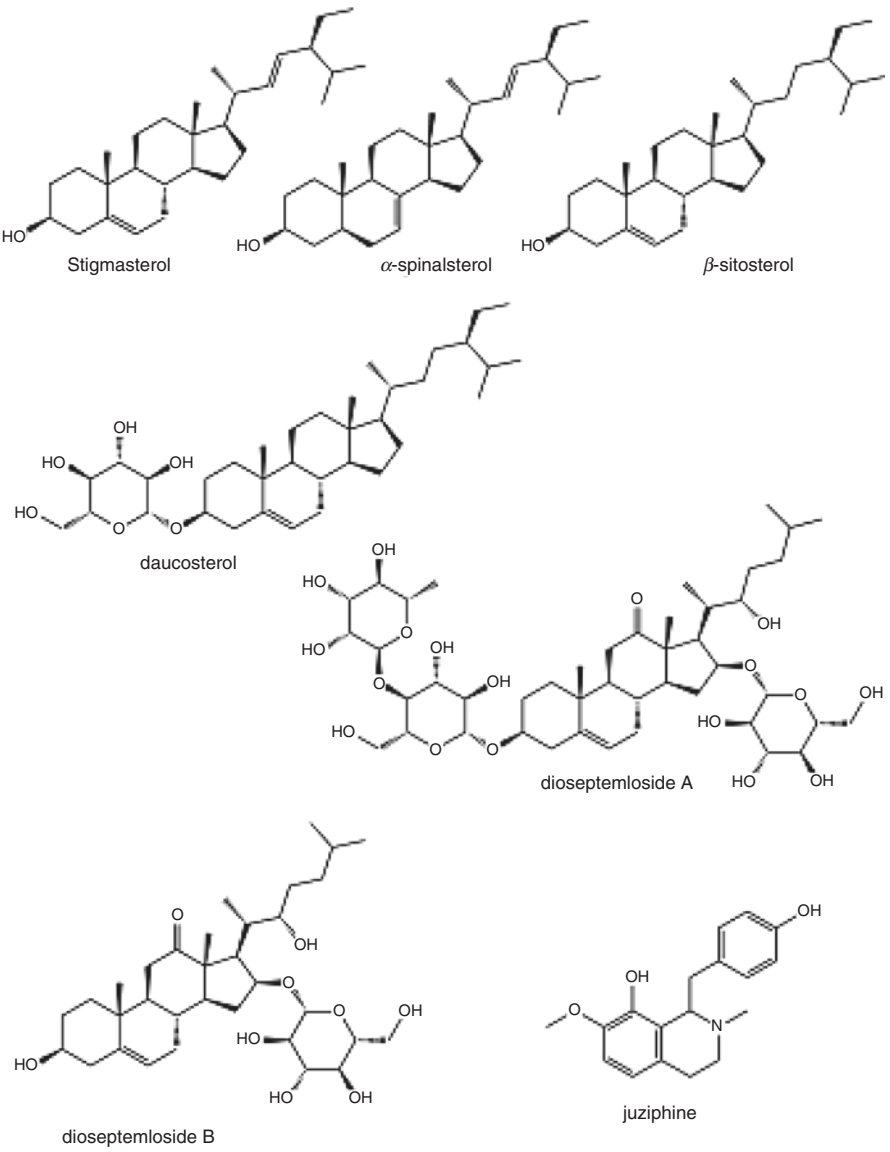

Fig. 8.1 (continued)

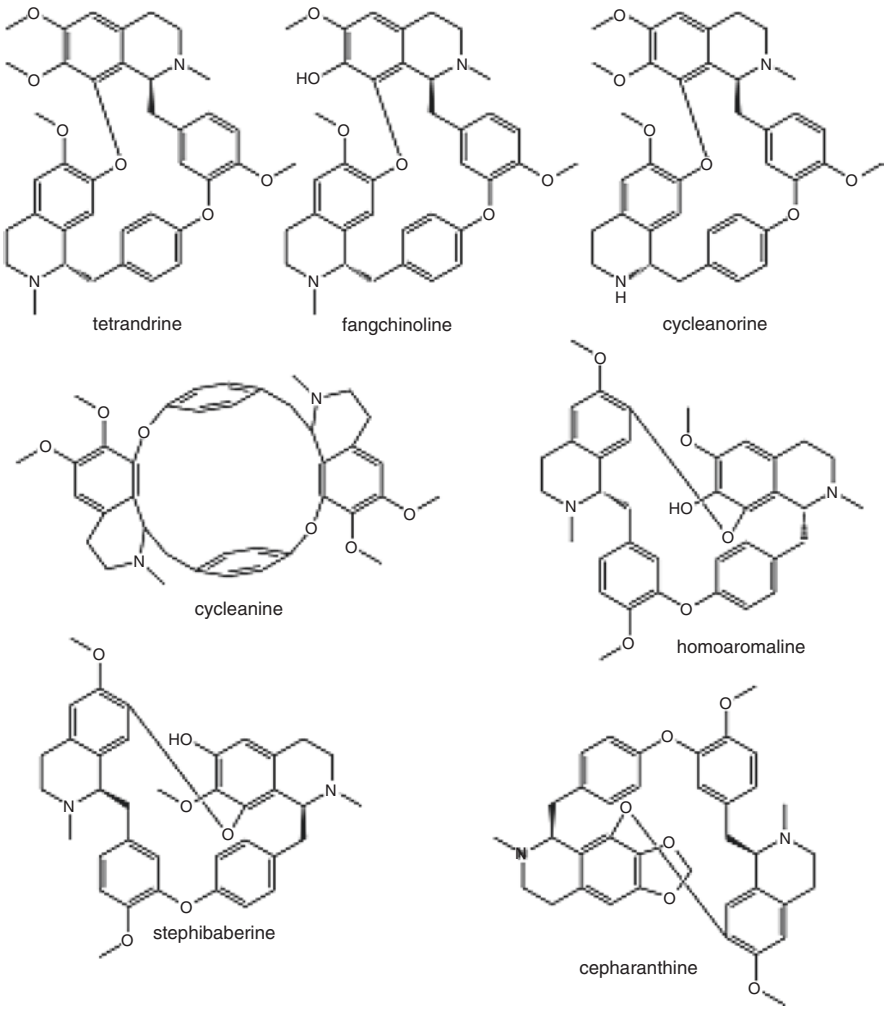

Fig. 8.1 (continued)

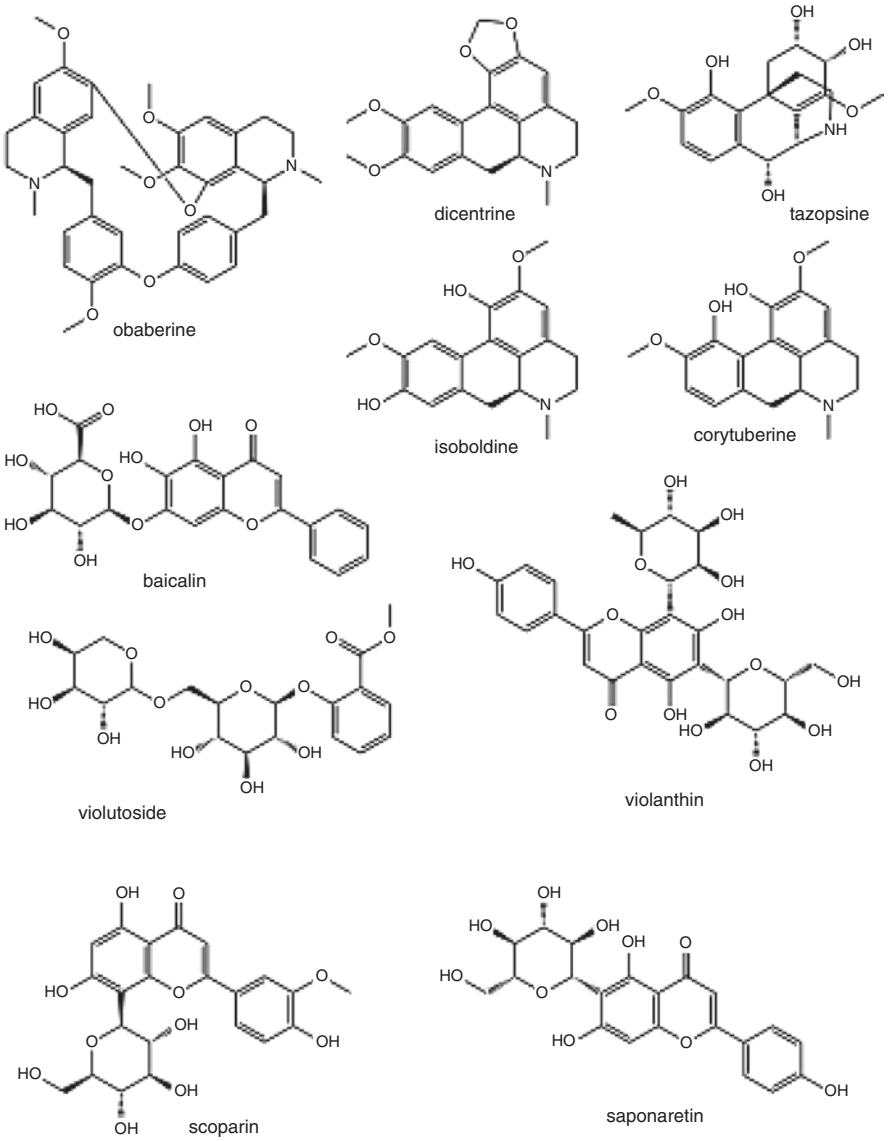

Fig. 8.1 (continued)

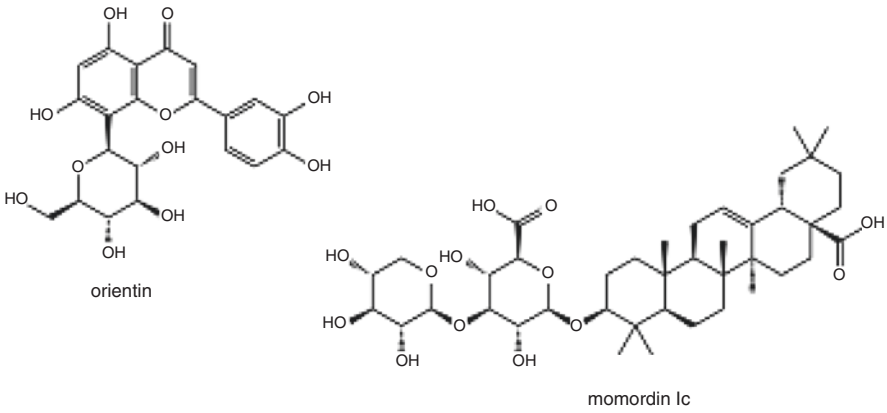

Fig. 8.1 (continued)

Patent number CN101366717A was filed on 2007-08-17 and granted on 2011-01-12. The invention relates to two successively applied medicinal preparations for treating condyloma acuminatum. The technical problem to be solved by the invention is to provide the two successively applied medicinal preparations for treating the condyloma acuminatum which can not damage normal tissues, are convenient to use and are effective. The compositions of a transdermal absorption type medicinal preparation are 30 to 80 weight percent of trichloroacetic acid homolog, 2 weight percent of water-soluble azone compound, 1 weight percent of menthol and the balance being water, wherein the azone compound comprises azone, Laurocapram, novel azone and derivatives of the azone, the Laurocapram and the novel azone and the trichloroacetic acid homolog comprises a trichloroacetic acid, a glacial acetic acid and derivatives of the trichloroacetic acid and the glacial acetic acid. The compositions of a coating medicinal preparation are 0.2 weight percent of glycyrrhetic acid, 2 weight percent of water-soluble azone compound, 10 weight percent of urea, 2 weight percent of nano-silver water solution and the balance being water. By utilization of the two medicinal preparations to coat affected parts, viruses can be eliminated, immunity can be strengthened and recrudescence can be prevented, thus the expected aims are achieved in practice." [https://patents.google.com/patent/CN101366717A/en].

Patent CN102716112B claims to resist HPV infection. The patent was filed on 2012-07-13 and granted on 2014-05-14. The medication is said to contain germacrone, furanodiene, curdione, β-elemene, curcumol, curzerene, and borneol. [https://patents.google.com/patent/CN102716112B/en].

Further information on Chinese patents for anti-HPV formulations can be found in "A61P 15 - Drugs for genital or sexual disorders; Contraceptives," which gives the entire list and description of patents in this area though the patents (55,635 patents) are not necessarily solely on anti-HPV or its symptoms but covers the whole gamut of the title described. [https://www.google.com/patents/sitemap/en/Sitemap/A61/A61P/A61P_15_22.html].

9 Toxicity of TCM Formulations and Drugs

TCM formulations have the reputation, whether actual or not, of being toxic, the toxicity ranging from zero to highly toxic. As with any traditional medicinal systems and natural product, particularly plant-based formulations, the toxicity allegations have some merit based on just common grounds. A given drug in low amounts can be beneficial for health or to cure disease(s); however, once a threshold limit has been crossed, the drug can be even fatal when taken above that threshold dose. This paradigm applies to even modern over-the-counter (OTC) drugs like paracetamol or aspirin. Both relieve pain, but the former can cause hepatotoxicity and the latter gastric ulceration. Plant secondary metabolites are the phytochemicals used as drugs because of their pharmacological effects. However, the concentration of such secondary metabolites can vary widely depending on the region of cultivation, climate, and stress factors like drought, excess water, or pest attack. As a result, if a drug consists of crude plant powder (as in many TCM formulations), the concentration of the principal bioactive secondary metabolite can differ to an extent where instead of curative, it produces a toxic effect.

Ueng et al. (1997) have pointed out several factors behind toxic effects in TCM medications; toxicity can be due to contamination with heavy metals, pesticides, or even addition of a Western medicine to a TCM drug. Adverse effects can occur from improper dispensing and individual idiosyncrasy. They also pointed out that many TCM products show mutagenicity in Ames test and also that various TCM medications can adversely affect organs like liver, kidney, gastrointestinal tract, and nervous and cardiovascular systems.

10 Conclusion

Human papilloma virus (HPV) infections can range from being totally harmless and going away in a few days by itself to causing a number of cancers, the most important being cervical cancer in women. HPV is more prevalent in the low-income countries because of lack of adequate diagnostic and treatment facilities, and it is possible that because of this and other undefined factors, HPV has not attained the attention it deserves. It is possible that traditional medicinal systems in a number of countries may be able to provide effective treatment for HPV infections, but traditional Chinese medicine (TCM) appears to be the most advanced and quite thorough in this area, taking into account HPV infection and its various ramifications, and the number of TCM formulations in existence to deal with the complications associated with HPV infections. However, a major problem with TCM is the lack of adequate

studies regarding toxicity and pharmacokinetics of a given formulation or a drug. Once these two problems are adequately addressed, TCM can play a major role in the treatment and even possible eradication of this viral disease in its various manifestations.

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