# In Vitro Production of Quinones

# 14

Ehab M. B. Mahdy, Sherif F. El-Sharabasy, and Maiada M. El-Dawayati

**Abstract**

Quinones as natural derivatives of phenolic constituents have a broad sense of biological activities, including anticancer, antimicrobial, anti-inflammatory, and purgative effects. Quinones have multiple applications such as dyes, pigments, cosmetics, food additives, flavors, agrochemicals, and pharmaceuticals. Those molecules have existed across the whole of organisms; plants are a prime natural source. Concerning the bio-based economy (bio-economy), a renewed push has been intended in the plant biotechnology area to crop high-value bio-ingredients for various downstream applications. Quinones divide into four classes along with a number of benzene rings: phenanthrenequinone, naphthoquinone, anthraquinone, and benzoquinone. The quinone molecules have to be interestingly investigated through their chemistry, classification, nomenclature, biosynthesis, biological effects, and distribution naturally in plants. We will here give an update on account of reports and studies done on bioactive quinones. The chemical structure with biological effects and biosynthesis will be the focus. Besides, we provide the progress on some significant plant-derived quinones and their mode of action to endorse more beneficial biologic features.

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## 14.1 Introduction

Plants biosynthesize a wide range of natural products that use dyes, pigments, cosmetics, food additives, flavors, agrochemicals, and pharmaceuticals (Malik et al. 2014a, b, c). These secondary metabolites are heterogeneous compounds and can generally survive and biosynthesize from a bewildering array of the environment (Lubbe and Verpoorte 2011) under specific conditions, viz., specific nutrition and abiotic stresses (Malik et al. 2010a, b, 2013). These metabolites require primarily a renaissance of natural products (Lu et al. 2020; Raskin et al. 2002); so, the world market is annually rising at a rate of 15–18%.

Secondary metabolites are divided primarily into three key groups: (1) polyphenols, (2) alkaloids, and (3) terpenes. Quinones, as derivatives from oxidization of hydroquinones or polyphenols (Eyong et al. 2013a, b; Gong et al. 2014), are biosynthesized across the whole of kingdoms (Hillion and Antelmann 2015; Widhalm and Rhodes 2016; Yamamoto et al. 2018). Plants are the prime source of quinones, which exist in a wide range of families, including Vitaceae, Arecaceae, Verbenaceae, Bignoniaceae, Fabaceae, Caesalpiniaceae, Rhamnaceae, Polygonaceae, Rubiaceae, Orobanchaceae, Boraginaceae, and Lamiaceae (Oni et al. 2015; Soladoye and Chukwuma 2012). The role of quinones in plants is still mostly mysterious. Quinones are often negligent in the research of signal agents (Widhalm and Rhodes 2016). Plants do not have homologs of recognized quinones sensor as in animals and bacteria that own cysteine amendments of receptor proteins, which affect cytoprotective gene expression (Yamamoto et al. 2018). They consequently are probable to use sensing strategies different from those of animals (Farmer and Davoine 2007). Plastoquinones, α-tocopherol quinones, and phylloquinone are mainly metabolites existing in all photosynthesizing cells. Ubiquinones are made in most species of plantae kingdom. The majority of quinones are simple benzoquinones, naphthoquinones, or anthraquinones. However, less common skeletal structures occur, for instance terpenoid quinones and higher polycyclic quinones. In nature, most quinones are *p*-quinones, nonetheless *o*-quinones also occur (Fig. 14.2).

Anthraquinones originate in a broad sense of families such as Rubiaceae, Fabaceae, Rhamnaceae, Polygonaceae, Liliaceae, and Scrophulariaceae. Most naphthoquinones accumulate in Bignoniaceae, Verbenaceae, Juglandaceae, Plumbaginaceae, Boraginaceae, Lythraceae, Balsaminaceae, Ebenaceae, and Droseraceae. Myrsinaceae and Borraginaceae that are most families accumulate benzoquinones.

Quinones are divided into four sorts according to the number of benzene rings: phenanthrenequinone, naphthoquinone, anthraquinone, and benzoquinone

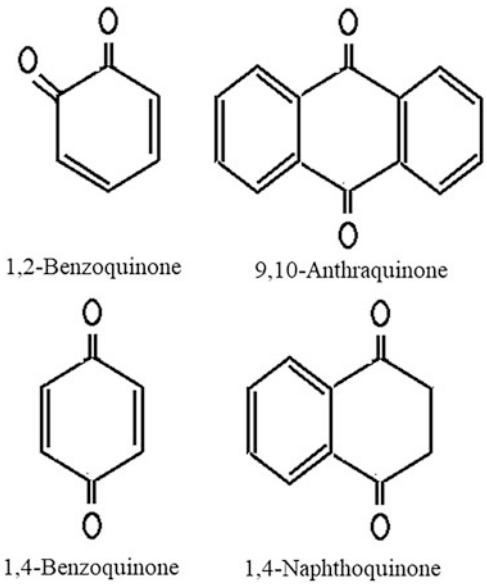


**Fig. 14.1** Structure of four classes of quinones

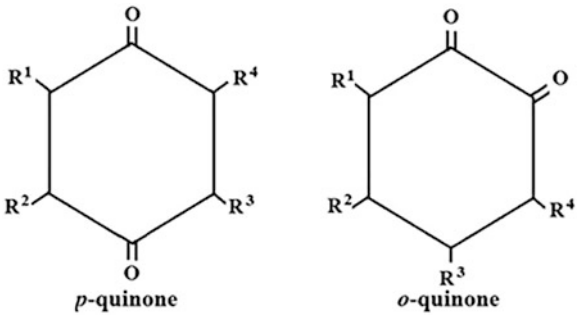


**Fig. 14.2** Structure of *para*-quinones (1) and *ortho*-quinones (2)

(Fig. 14.1). Quinones play a prime role, as a signal agent, of biological activities, i.e., anticancer activities, antibacterial activities, food additives, and purgative effects (Aithal et al. 2009, 2011; Padhye et al. 2012). The compound 2,6-dimethoxy-1,4-benzoquinone (DMBQ) is only well-documented in the induction of haustoria across parasitic roots. Nevertheless, the sense of DMBQ is still blurred.

Focusing on the bio-economy (biological-based economy) has increasingly meant a modern drive in the biotechnology approach to yield high-value biomaterials for several downstream applications. Bio-economy emphasizes maintainable ('green') manufacture of renewable bio-resources and their change into value-added products in food, feed, chemicals, energy, and healthcare and wellness. Secondary metabolites have always been the prime source of biomaterial for many medicinal and manufacturing applications (Chakraborty 2018; Misra 2014; Nomura et al. 2018; Owen et al. 2017; Xin et al. 2017; Yang et al. 2016).

We will highlight the progression of some significant quinone derivatives, their chemistry, biosynthesis pathways, mode of action, and in vitro production. Besides, biological activities and scale-ups have considered encouraging more valuable biologic properties.

## 14.2 Biosynthesis Pathway

Biosynthesis is a dynamic method to get quinones and it is obligatory to reconnoiter the pathway and sense the mechanism of the mode of actions. Numerous quinone derivatives were reported (Camelio et al. 2015; Eyong et al. 2013a, b; Gong et al. 2014). The complementary aspect in the biosynthesis of bioactive products is to clarify their pathways. Quinones are naturally among the most miscellaneous biometabolites; however, they are almost all biosynthesized through the mevalonate pathway or 2-C-methylerythritol 4-phosphate (Nowicka and Kruk 2010; Pina et al. 2016; Skorupinska-Tudek et al. 2008; Socaciu 2007; Widhalm and Rhodes 2016). Two main pathways regulate the biosynthesis of natural products. By C13 labeling experiments, isopentenyl diphosphate (IPP) could switch between both pathways and contribute to the consequent biosynthesis pathways (Skorupinska-Tudek et al. 2008). The acetyl-coenzyme A (Co-A) units are a start step of the biosynthesis pathway, which catalyze acetyl-CoA C-acetyltransferase (AACT) to produce acetoacetyl-Co-A. The gene encoding AACT was cloned successfully from *Tripterygium wilfordii* (Zhao et al. 2015a, b). Liu et al. (2014) cloned the gene encoding 3-hydroxy-3-methylglutaryl-CoA synthase. Wu et al. (2012a, b) characterized the gene encoding NADPH-dependent HMG-CoA reductase (HMGR). Mevalonate pathway is gone down into IPP through subsequent chains of enzymes (Zhao et al. 2013). The IPP catalyzes to dimethylallyl pyrophosphate (DMAPP) using IPP isomerase. Both substrates are commonly for two pathways (Drummond et al. 2019). Pyruvate substrates are significant in the pathway of 2-C-methylerythritol 4-phosphate (Lichtenthaler 1999). Two genes, encoding 1-deoxy-D-xylulose-5-phosphate synthase (DXS) and 1-deoxy-d-xylulose-5-phosphate reductoisomerase (DXR), can be expressed highly in roots of *T. wilfordii* cloned (Tong et al. 2015a, b, c; Zhang et al. 2020). IPP isomerase catalyzed the conversion of IPP and DMAPP and was joined by protonation and deprotonation reactions (Xiang et al. 2010; Zhang et al. 2015; Zhao et al. 2015a, b; Tong et al. 2016). Cloning and expression of the MEP pathway were screened by the enzyme-encoding genes in *Osmanthus fragrans* (Xu et al. 2016). Zhou et al. (2018) identified the functions of five squalene epoxidase (SE) genes of *T. wilfordii* by *erg*1 mutant yeast constructed using CRISPR/Cas9.

Quinones properties are based on the structure of the chemical and aromatic ring, side-chain groups. Quinones, which have the aromatic di-one or di-ketone system in all creatures, can be substituted both in para- or ortho-patterns (R1 – R4) of its hydroquinone precursor (Fig. 14.2) (Weaver and Pettus 2014). So, quinones come from the corrosion of hydroquinones or polyphenols (Eyong et al. 2013a, b; Gong et al. 2014). Based on ring structure, quinones are classified into (1) benzoquinone

(1-ring structure), (2) naphthoquinone (2-ring structure), (3) anthraquinones, and (4) anthraquinones (Eyong et al. 2013a, b; Gong et al. 2014).

More intensive efforts are required to expand and progress the insight into biosynthetic processes. Biosynthesis pathway must be clear by illustrating the pathway of enzymes with their information and defining each intermediate. Biosynthesis pathways of quinones have stated various features of biosynthesis research (Kristensen et al. 2020). Quinones come from acetate/malonate (polyketide), iso-chorismate/*o*-succinylbenzoic acid, and p-hydroxybenzoic acid (Nowicka and Kruk 2010; Socaciu 2007; Widhalm and Rhodes 2016).

Plastoquinones, α-tocopherolquinones, and phylloquinone are primary metabolites existing in all photosynthesizing cells. Ubiquinones are present in the most species of plantae kingdom. The majority of quinones are majority of simple benzoquinones, naphthoquinones, or anthraquinones, although less common structures occur, such as higher polycyclic quinones and terpenoid quinones. Quinones, in nature, are *p*-quinones, or *o*-quinones. Anthraquinones accumulate in Rubiaceae, Fabaceae, Rhamnaceae, Polygonaceae, Liliaceae, and Scrophulariaceae; naphthoquinones accumulate in Bignoniaceae, Verbenaceae, Juglandaceae, Plumbaginaceae, Boraginaceae, Lythraceae, Balsaminaceae, Ebenaceae, and Droseraceae; while, benzoquinones accumulate in Myrsinaceae and Boraginaceae. Benzoquinones biosynthesize by the acetate/malonate or shikimic acid pathways. The gentisic acid (quinol form) is a side product formed by the oxidation of gentisaldehyde in the biosynthesis of putalin. The quinol forms biosynthesize naturally and most isolated benzoquinones are artifacts. Few families have been exhaustively investigated and led to the isolation of a few naphthoquinones and their glycosides. The 7-methyljuglone coming from Droseraceae and Ebenaceae is biosynthesized by the acetate-malonate pathway. However, composites without methyl groups are biosynthesized by the shikimic acid pathways, a situation that parallels that of the acetate-derived 6-methyl-salicylic acid and shikimate-derived salicylic acid. 3-chloroplumbagin, the chlorinated compound isolated from Plumbago (Plambaginaceae) and *Drosera* species (Droseraceae), should initiate a polyketide.

Anthraquinones biosynthesized through two pathways, one of which is emodin, with substituents in both rings A and C, are usually acetate-derived plants (lower and higher plants). Alizarin and its derivatives, without substituents in ring-A, are biosynthesized by the shikimic acid pathway. However, pachybasin from the fungus is acetate-derived, despite the absence of substituents in ring A.

Naphthoquinones started from two different precursors of pathways summarized in Fig. 14.3. Naphthoquinones (shikonin) have a wide variety of metabolites starting from simple compounds like 5-hydroxy derivative juglone to pigments with isoprenyl attachment such as alkannin. The precursor of 4-hydroxybenzoic acid (4HB) is composed of the shikimate and the phenylpropanoid pathway. The precursor of isoprenoid, geranyldiphosphate (GPP), comes from the mevalonate pathway (Zhang et al. 2015). In the first intermediate in shikonin biosynthesis, the 4HB geranyltransferase reaction binds the 4HB precursor to the isoprenoid (GPP) precursor and gives 3-geranyl-4-hydroxybenzoate (GBA). Two enzymes that regulate

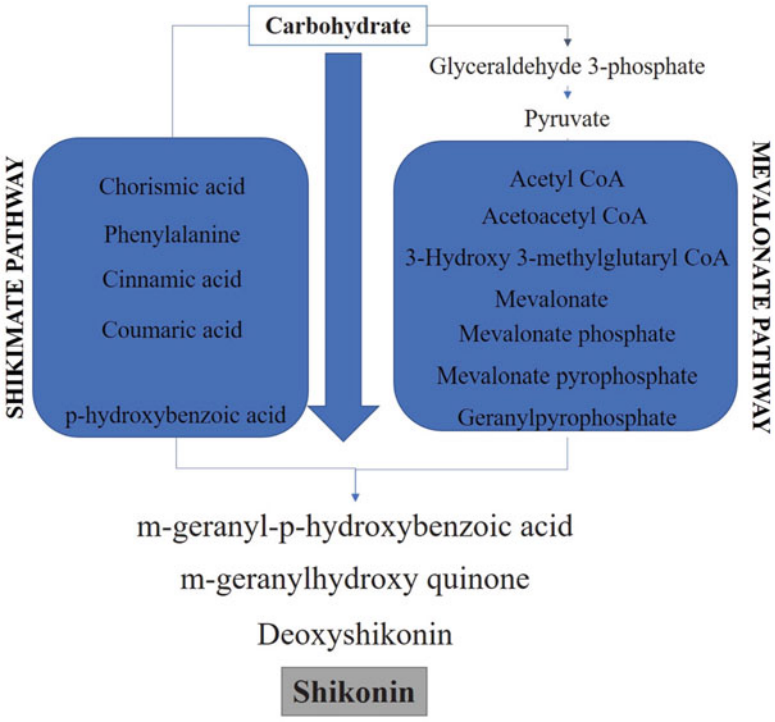


**Fig. 14.3** Pathways in Shikonin biosynthesis

shikonin biosynthesis pathways are hydroxyl-3-methylglutaryl co-enzyme-A reductase (HMGR) and 4HB geranyltransferase (Wu et al. 2012a, b). Phenylalanine ammonia-lyase (PAL) and 3-hydroxyl-3-methylglutaryl-CoA-reductase own high activities on biosynthetic enzymes of shikonin from *L. erythrorhizon* (Srinivasan and Ryu 1992).

In eukaryotes, ubiquinone and plastoquinone function manner-oxygenic electron-transport in photosynthesis and the aerobic respiratory chain (Liu and Lu 2016; Malik et al. 2014a, b, c). The quinones function to go with reversible $2e^{-}$ redox reactions, which protect the cells against free radicals and other potentially harmful oxidants (Kristensen et al. 2020; Liu and Lu 2016; Malik et al. 2014a, b, c).

## 14.3 In Vitro Production Methodology

Recent plant biotechnological approaches may offer an opportunity to overwhelm variation obstacles against the biotic/abiotic stresses, genetic manipulation, and production of metabolites (Kumar et al. 2011a, b; Malik et al. 2011a, b, 2014a, b, c). Quinones production might be in vitro supportive to understand well the biosynthesis pathway of metabolites. Plant tissue culture (PTC) has totipotency

**Table 14.1** Works on quinones production via PTCs

| Species | Method | Reference |
|---|---|---|
| *Lithospermum erythrorhizon* | | |
| | Cell suspension<br>Callogenesis<br>Organogenesis and embryogenesis | Yamamoto et al. (2000), Lin and Wu (2002), Yamamoto et al. (2002), Yu et al. (1997) |
| *L. canescens* | | |
| | Organogenesis | Sykłowska-Baranek et al. (2012) |
| *Echium lycopsis* | | |
| | Callus cultures | Fukui et al. (1983) |
| *A. Euchroma* | | |
| | Cell culture<br>Direct regeneration<br>Cell suspension<br>Callogenesis | Zakhlenjuk et al. (1993), Sokha et al. (1996), Ji and Wang (2001), Malik et al. (2010b), Zhang et al. (2013), Pietrosiuk et al. (1999), Sharma et al. (2008), Malik et al. (2010b), Bulgakov et al. (2001) |
| *A. hispidissima* | | |
| | Cell culture | Jain et al. (1999), Shekhawat and Shekhawat (2011) |
| | Organogenesis | Singh et al. (2002), Chaudhury and Pal (2010) |
| | Callus suspension | Shekhawat and Shekhawat (2011) |
| *Arnebia* sp. | | |
| | Cell suspension | Gupta et al. (2013) |
| *Onosma paniculatum* | | |
| | Cell suspension | Wu et al. (2009) |
| *E. italicum* | | |
| | Cell culture | Zare et al. (2010) |
| | Callogenesis | Zare et al. (2011) |
| *Rheum emodi* wall | | |
| | Organogenesis | Malik et al. (2010a, b) |

under complete-control conditions, in which exploiting is in the direction of interests. The PTC was exercised for multipurposes. Various reports used various explants on a broad sense of species (Malik et al. 2011a; Nosov 2012). The production of bioactive metabolites characterizes annually more consumption in different fields. PTCs take advantage of meeting the need for metabolites far away from the traditional extraction methods by intact plants (Nosov 2012). Many reports have accumulated and produced quinones through PTC. The chronicle investigations of quinone production via in vitro tissue cultures are highlighted in Table 14.1. They used different ways such as exposure to elicitors/inducers, precursors, plant growth regulators (PGR) concentrations, and basal media, e.g., Murashige and Skoog (1962) media and Linsmaier and Skoog (1965). Shikonin derivatives and pyrrolizidine alkaloids are isolated from *A. euchroma* (Pietrosiuk et al. 1999, 2006). Sharma et al. (2008) reported acetylshikonin and b-acetoxyisovalerylshikonin through cell suspension proliferation. Jain et al. (1999) produced arnebins from *the A. hispidissima* plant. Some compounds'

isolation such as isohexenylnaphthazarin has been proved through cell suspension cultures of *A. euchroma* (Damianakos et al. 2012).

However, few bioactive compounds have been made marketable or got to industrial-scale via PTCs. Numerous efforts have been concentrated on increasing the scale-up production by separating the biosynthetic activities based on choosing proper explants, optimizing the nutrient media, and optimizing the PGRs' concentration and proliferation conditions (Bulgakov et al. 2001; Malik et al. 2008, 2009, 2011a, b; Zare et al. 2011 Zhang et al., 2013). The TDC1 and TDC3 isoforms are induced via abiotic and biotic stress factors in rice (Dharmawardhana et al. 2013).

Various genera belonging to the Boraginaceae family showed a 10% higher content of acetylshikonin and isobutrylshikonin (Pietrosiuk et al. 2006). Alkannin contents accumulated on half-strength agar-solidified MS medium from hairy roots of *A. hispidissima* induced with *A. rhizogenes* (Singh et al. 2002). The functions of guaiacol peroxidase (G-POD), ascorbate peroxidase (APX), and catalase (CAT) at quarter strength (0.25) of MS media-treated root tissue culture of *Morinda citrifolia* were efficient to remove the probable hazard of hydrogen peroxide (H2O2). Baque et al. (2010) demonstrated lowing the accumulation of H2O2 and the level of lipid peroxidation.

Photo-protection as free radical hunters and carotenoids are the precursors for quite a few physiological apocarotenoids (Auldridge et al. 2006; Bouvier et al. 2005) like the phytohormone abscisic acid (ABA), originating from 9-cis-violaxanthin, and 9-cis-neoxanthin (Qin and Zeevaart 2002).

The main complex problem is the impact of turbulence through the scale-up of PTC (Busto et al. 2008; Busto et al. 2013). The impact of unrest and light on cell feasibility, biomass, and anthraquinones production has been measured by Busto et al. (2013). The biomass concentration and anthraquinones production were similar to the achievement of Busto et al. (2008) on *R. tinctorum* suspension cultures by a stirred tank bioreactor. Scheme of simple and downscaled culture proliferation is a valid scale-up for inducing anthraquinones through PTCs.

## 14.4 Scale-up Techniques and Bioreactors

For long decades, many efforts have been commercially allowed to produce quinone derivatives using PTCs based on the optimizing of media, environment conditions, and downstream parameters. The Mitsui Petrochemical Co., Japan, is one of the first companies in the shikonin production on the commercial scales. The quinone production has fruitfully scaled up using bioreactors. Those productions by PTC and bioreactor technologies have highly accumulated quinones 20–30% rather than the intact plants, which yielded in a few years in only a few days 3–6% (Ge et al. 2006; Renneberg 2008). Several investigations were proceeded to understand well how quinone derivatives are biosynthesizing and their mode of action. Shikonins are produced by changing the biosynthesis pathway (Sommer et al. 1999). The biosynthesis has identified the path of shikonins (Singh et al. 2010). Zhang et al. (2011) characterized that the gene LeERF-1 in *L. erythrorhizon* downregulated shikonin by

light optimization. Factors affecting low energy ultrasound (Lin and Wu 2002), physicochemical effects (Malik et al. 2011a, b), and selection of PFP-resistant cell lines (Zakhlenjuk et al. 1993) have been considered (Shekhawat and Shekhawat 2011; Sykłowska-Baranek et al. 2012; Zare et al. 2010, 2011). Zhang et al. (2013) studied the effects of fungal elicitor on accumulation of shikonins.

## 14.5 Extraction and Detection Techniques

Advancement in phytochemical approaches has witnessed a progression in isolating and detecting biometabolites. Phytochemical methods have been utilized (Mboso et al. 2013; Obadoni and Ochuko 2001; Sofowora 1993; Soladoye and Chukwuma 2012). HPLC is a universal tool to detect secondary metabolites in plants.

### 14.5.1 Extraction and Isolation of Quinone Compounds

The best tissue for isolating quinone derivatives could be extracted from any part of the tissue based on natural constituents, a species, age of tissue, and existing interest-accumulated tissues.

**Box 14.1 Extraction of Quinone Derivatives**

- Dry and fine-powder of tissues (200–300 g).
- Dissolve with 500 mL a proper solvent (hexane, chloroform, and ethyl-acetate) using Soxhlet; then filter.
- Subject to column chromatography over silica gel via the gradient elution.
- Read on high-performance liquid-chromatography (HPLC).

Standard quinones are isolated from samples (Box 14.1) that should be fine-powdered and dry well. Proper solvents, including hexane, chloroform, and ethyl acetate, are subjected to using Soxhlet extractions to obtain extracts via column chromatography over silica gel using gradient elution method (Singh et al. 2005). Ethyl acetate extracts on column purification with methanol–chloroform (20:80, v/v) produced emodin glycoside and chrysophanol glycoside. Chloroform extract on column purification with ethyl acetate-hexane (30:70, v/v) cropped emodin, while hexane extract on column purification with ethyl acetate-hexane (5:95, v/v) borne chrysophanol and physcion (Singh et al. 2005). Quinone derivatives scored via spectrophotometer, analyzed using ultra-performance liquid chromatography (UPLC), and compared with the reference values (Coskun et al. 1990; Kubo et al. 1992;Semple et al. 2001; Yang et al. 2016). Plastoquinones, α-tocopherol quinones, and phylloquinone are prime metabolites presenting in all photosynthesizing tissues. Ubiquinone is found in most genera. The quinones, which are prime in plants, are relatively simple benzoquinones, naphthoquinones, or anthraquinones. Skeletal

structures of quinones are also found, for instance, terpenoid quinones and higher polycyclic quinones.

### 14.5.2 Determining Quinone

**Box 14.2 Anthraquinone Determination**

- Soak 50 mg of the sample in 50 mL of dH2O/16 h.
- Heat sample suspensions at 70oC/1 h in water bath; then cool.
- Add 50 mL of 50% to the sample; the filter.
- Read the spectrophotometric value at a 450 nm.
- Compare with a standard (1 mg/100 mL).

Anthraquinone derivatives could be spectrophotometrically determined as described in Box 14.2, according to Zenk et al. (1975) and Soladoye and Chukwuma (2012). Quinones scored via spectrophotometer, analyzed using high-performance liquid chromatography (HPLC), and compared with the reported values (Semple et al. 2001; Yang et al. 2016).

### 14.5.3 Genetic Approaches to Detect Quinones

The progression in genetic tools is utilized rapidly for a broad sense of biological disciplines. Low production of quinones by PTC is a chief bottleneck at commercial scales (Charlwood and Pletsch 2002). Therefore, genetic tools, e.g., genetic engineering, can be probable to be employed for regulatory steps of biosynthetic pathways to high-yield content of constituents' scales (Charlwood and Pletsch 2002). Quinone transformation via *Agrobacterium rhizogenes* to promote the bioactive compounds has been stated. Those have been very evidenced genetic stable with rather than 10–20% quinones production such as acetylshikonin and isobutrylshikonin (Boehm et al. 2000; Kohle et al. 2002; Pietrosiuk et al. 2006). Pietrosiuk et al. (2006) produced ca. at higher 10% acetylshikonin and isobutrylshikonin of *L. canescens* hairy roots than natural roots.

Several investigations on genetic and biochemical approaches had found that the 1,4-naphthalenoid ring started from the pathways of shikimate and *o*-succinylbenzoate. Genetic manipulation of various regulatory factors takes advantage of tolerance mechanisms of stress in species. Numerous genes were biosynthesized quinone pathways in a broad sense of species. Gene expression analysis of bioactive constituents may be an additive or inhibitory effect on the expression of PGR actions (Dharmawardhana et al. 2013; Pelagio-Flores et al. 2011). The family of *ubi* genes has a primary role in biosynthesizing quinone pathways (Kohle et al. 2002). The *ubi*A gene has not expressed the shikonin across *L. erythrorhizon* tissue culture (Boehm et al. 2000), whereas quinones have

transformed with HMGR cDNA and shown high activity using callogenesis of *A. euchroma* (Malik et al. 2014a, b, c). The genetic manipulation of the biosynthesis pathway accumulated high quinone through PTCs (Kohle et al. 2002; Sommer et al. 1999).

Dihydroorotate:quinone oxidoreductases (DHOQO) are membrane-bound enzymes for oxidizing dihydroorotate (DHO) orotate with concomitant reduction of quinone to quinol. de Sousa et al. (2020) concluded the DHOQOs could be the single dihydroorotate dehydrogenase or could exist with other dihydroorotate dehydrogenases (DHODH), as the NAD+ or fumarate reducing enzymes. Stimulation of different overexpression of genes or suppression regulation could affect the quinones biosynthesis (Malik et al. 2014a, b, c). Freshly, Next Generation Sequencing (NGS) analysis applicable on tissue culture-infected Chardonnay propagules exhibited some genes responsible for photosynthesis process under both light and dark phases that were downregulated (Bertazzon et al. 2019).

## 14.6 Biological Activities (Major)

Investigations on various biological properties, e.g., medical, pharmaceutical, and other industrial activities, have been shown (Oliveira et al. 2020; Prateeksha et al. 2019). A broad sense of biological activities has been recognized as natural therapeutic and dying properties. Previous reviews reported numerous activities, including antioxidant, anti-ulcer, anti-inflammatory, anticancer, neuroprotective, antiaging, lung protective, and hepatoprotective properties (Choi et al. 2005; Prateeksha et al. 2019; Singh and Chauhan 2004). Plant extracts possess antineoplastic properties and hepatoprotective activity and own the Ayurvedic system using anti-PAF (platelet-activating factor), immunomodulant, blood purifier, and anti-inflammatory. Other extracts from *R. yunnanensis* enhance the ATP magnitude of both brain and heart, an increase of leukocytes, and the treatment of psoriasis (Singh and Chauhan 2004). Major biological investigations are detailed below. Various reports have generally shown the changes in metabolites due to the detrimental infection impacts at molecular and physiological levels (Margaria et al. 2014; Oliveira et al. 2020; Prezelj et al. 2016). Those are due to the extreme gathering of carbohydrates, phenolics, and chlorophyll deficiency (Oliveira et al. 2020; Prezelj et al. 2016). Accumulations such as high starch in leaf mesophylls are leaded to accompany through upregulation of prime genes with their biosynthesis (Hren et al. 2009; Margaria et al. 2014; Oliveira et al. 2020; Prezelj et al. 2016). Anthocyanins detected in micropropagation-infected cv. 'Barbera' leaf propagules and transcript genes of the flavonoid pathway and pro-anthocyanidins were higher in infected plants (Hren et al. 2009). Photosynthesis is the key sponsor of redox equivalents and energy that provides amino acids, secondary metabolites, and carbohydrates (Allahverdiyeva et al. 2015; Margaria et al. 2013; Oliveira et al. 2020; Vitali et al. 2013). Tocopherols perform protecting PSII from photoinactivation and membrane lipids from photooxidation (Allahverdiyeva et al. 2015; Havaux and García-Plazaola

2014). Isoprenoids are vital electron transporters acting in oxidative phosphorylation and photosynthesis (Ducluzeau et al. 2012; Havaux and García-Plazaola 2014).

### 14.6.1 Chrysophanol

Many quinones possess antidiabetic activity (Prateeksha et al. 2019; Singh and Chauhan 2004). Chrysophanol activity signalizes mainly insulin. It lowers postprandial hyperglycemia by approximately a half percent of the bodyweight of the albino rat (Arvindekar et al. 2015; Choi et al. 2005). This compound served as inactive in contradiction of intestinal alpha-glucosidase enzyme (Arvindekar et al. 2015; Lee and Sohn 2008); as well enhanced the phosphorylation of insulin receptor substrate-1 (IRS-1) through an aggressive impact on its inhibitor, protein-tyrosine phosphatase 1B (PTP-1B) (Arvindekar et al. 2015; Prateeksha et al. 2019). Chrysophanols could raise the phosphorylated-activated protein kinase-B (P-AKT) level in human-liver carcinoma cells (Onoda et al. 2016). Chrysophanol with the peroxisome proliferator-activated receptor (PPAR-γ) might perform against PPAR-γ expressing in adipose tissue and regulates the metabolism of lipid and glucose (Onoda et al. 2016). More articles at the scale of in vitro, in vivo, and in silico assays may provide a useful direction to confirm the agonistic effect on PPAR-γ and DPP-IV (Arvindekar et al. 2015;Onoda et al. 2016; Prateeksha et al. 2019).

Anticancer properties have been established by several investigations via necrosis, a caspase-independent phenomenon, which causes unalterable inflammatory sense against tumor cells (Onoda et al. 2016; Prateeksha et al. 2019). Chrysophanols have lowered the cell viability of liver cancer by necrosis through a proper concentration and incubation time (Lu et al. 2010). Apoptosis-associated signals, including the loss of mitochondrial membrane potential (MMP), raise the reactive oxygen species (ROS), cytosolic Ca + 2, and the release of cytochrome c from mitochondria. It delays the externalization of phosphatidylserine in chrysophanol-treated liver cancer and indicates apoptosis. Extra levels of apoptotic signal-associated proteins, for instance, apoptosis-inducing factor (AIF), were lowered in the treated cells (Lu et al. 2010). Correspondingly, chrysophanol affects cell viability in renal cancer and lung cancer (Choi 2016; Ni et al. 2014). Also, chrysophanol cytotoxicity detected contra human breast cancer and leukemia cells (Choi et al. 2007; Kang et al. 2008; Sun et al. 2014). Chrysophanol has a potential against antagonistic to MYLK4 and affects metastasis and tumor invasion (Demirezer et al. 2016; Lee et al. 2011).

The protective effects of quinones inspected (Lin et al. 2015; Prateeksha et al. 2019) on lipopolysaccharide (LPS)-induced inflammatory and the oxidative response of murine microglial cells were explored [95]. Likewise, the effect on the hippocampus of lead-poisoned neonatal mice was spotted, in which chrysophanol diminished the hippocampal injury and enhanced the learning memory through encouraging the cell-defense system of antioxidants. The lead-exposed neonatal rat has lowered dose-based means in the heart, spleen, liver, kidney, brain, and blood (Lin et al. 2015; Yan et al. 2014; Zhang et al. 2014). The action of chrysophanol on

cerebral ischemic stroke through endoplasmic reticulum stress was illuminated (Zhang et al. 2014; Zhao et al. 2016). Chrysophanols have the probability to reduce retinitis pigmentosa (RP), an inherited photoreceptor-degenerative disease. It inhibited apoptosis, gliosis, activation of microglia, and matrix metallopeptidase 9 (MMP-9) expression in N-methyl-N-nitrosourea (MNU)-induced mouse model of RP (Lin et al. 2017; Prateeksha et al. 2019).

Chrysophanol has hepatoprotective effects (Jiang et al. 2016). It regulates inflammatory sensing brought in mice via hepatic injury. The block of caspases-associated apoptosis induction indicated to chrysophanol could shield in contradiction of liver injury by its antiapoptotic effect (Jiang et al. 2016). Hepatoprotective activity via chrysophanol lowered the gamma-glutamyl transpeptidase (GGT) activity that necessitates GSH homeostasis. The immunoblot analyses decrease in the expressions of cytochrome, GGT, and GSH (Jiang et al. 2016; Qian et al. 2011). Some reports suggested that the chrysophanol could save against the gastrointestinal effects of cold-resistant ulcers, alcohol, aspirin, and pyloric ligation-induced ulcer in mice (Suleyman et al. 2004). Chrysophanols have decreased the acids through the inhabitation of H+/K + -ATPase activity. Nevertheless, its activity shows less than the emodin molecule. Upregulation of mucin secretion, a protect mechanism of the ulcer, is also noted in chrysophanol-treated rats.

Regarding the activities of anti-inflammatory, various essays stated the mode of defense action via chrysophanol in numerous diseases (Malik and Muller 2016). The effects of chrysophanol on dextran sulfate sodium (DSS)-induced colitis and LPS-induced inflammatory were sensed by Kim et al. (2010) in rats' peritoneal macrophages. Furthermore, chrysophanol significantly removes atopic dermatitis that rises in phosphorylated-mitogen-activated protein kinase. This active constituent, AST2017-01, is a potent anti-inflammatory of konsentrasi hambat minimum (KHM) or functional food (Jeong et al. 2018). Carrageenan, histamine, dextran, serotonin formaldehyde-induced edema tests, cotton-pellet granuloma, and Kabak tests could be used to examine anti-inflammatory in mice (Jeong et al. 2018; Suleyman et al. 1999).

The activity of chrysophanol has shown anti-microorganisms, e.g., viruses (Bunluepuech et al. 2016; Chang et al. 2014; Ramana et al. 2017), fungi (Choi et al. 2004; Liu et al. 2009; Malik and Muller 2016; Ren et al. 2012), and bacteria (Rodrigues et al. 2017; Singh et al. 2017).

Numerous pharmacological activities on chrysophanols are recognized. This molecule is an antiprotozoal factor agonist chloroquine-resistant and sensitive to *Plasmodium falciparum* strain (Abdissa et al. 2017). The molecule chrysophanol is demonstrated as an anti-obesity response to recover pulmonary injury in mice through advanced anti-inflammatory and antioxidant retort to injured tissue (Li et al. 2016). Also, it inhibits triglyceride and cholesterol in the fish zebra, which is on a high cholesterol diet. Antituberculosis affects *Mycobacterium tuberculosis* and *M. bovis* (Schorkhuber et al. 1998). The antinomic activity of chrysophanol against root-knot nematode was also testified (Tripathi et al. 2014). Likewise, chrysophanols are the main constituents of various species such as Cassia and Aloe owning the laxative effect (Malik and Muller 2016).

### 14.6.2 Aloe-Emodin (AE)

Quinone of AE is a bioactive hydroxyanthraquinone, which exists in a broad spectrum of medicinal plants, having laxative, antifungal, antiviral, anticancer, and hepatoprotective activities (Agarwal et al. 2000; Arosio et al. 2000). The modes of human cancer contain various carcinoma cells which include nasopharyngeal carcinoma, lung cancer, leukemia, neuroectodermal tumor, colon cancer, and hepatocellular carcinoma (Lee et al. 2006; Lin et al. 2010, 2011; Pecere et al. 2000; Suboj et al. 2012). AE-induced cancer cell cultivating inhibition is produced by prolonged G1, S, or G2/M phase cell cycle capture or apoptosis based on the tissues and treatment procedure (Guo et al. 2007, 2008; Xiao et al. 2007). This remarkably prevents chorioallantoic membrane angiogenesis and inhibits tubule formation of endothelial cells on matrigel (Cardenas et al. 2006; Chiu et al. 2009). AE suppresses cancer cell migration, invasion, and metastasis (Chen et al. 2010a, b; Tabolacci et al. 2010). Moreover, antiproliferative effects come by the linkage of 5-fluorouracil, doxorubicin, tyrosine kinase, and the cisplatin inhibitor (Fenig et al. 2004).

AE encourages DNA damage and obstructs DNA repair gene expression in cancer cells akin to the promotion of reactive oxygen species (ROS) (Lee et al. 2006). It downregulates cyclin A, cyclin-dependent kinase 2 (CDK2), protein kinase C (PKC), and c-Myc as well as upregulates cyclin B1, CDK1, p53, and p21 (Chiu et al. 2009; Guo et al. 2007, 2008). The c-Jun N-terminal kinase (JNK) activation (Lu et al. 2007), p53 pathway, Fas pathway, and caspase activation are mechanistically involved in aloe-emodin-induced apoptosis (Chiu et al. 2009; Pecere et al. 2003). Aloe-emodin also performs the following activities: decreases the levels of urokinase (Cardenas et al. 2006); suppresses the expression of metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9) (Chen et al. 2010a, b; Tabolacci et al. 2010); as well locks up translocation and the binding of DNA binding (Suboj et al. 2012).

Other hydroxy-anthraquinones, like emodin, rhein, and chrysophanol, own anticancer effects. Their mode of action is akin to those of AE (Cha et al. 2005; Chun-Guang et al. 2010; Lu et al. 2010; Shi et al. 2008; Tan et al. 2011). Further, some derivatives such as 1,8-Di-O-alkylaloe-emodin and 15-amino-emodin, 15-thiocyano-emodin, and 15-selenocyanochrysophanol initiated from AE might show potential to the cytotoxic effects on cancer cells (Cui et al. 2008).

### 14.6.3 Juglone

Juglone is isolated from *Juglans mandshurica* Maxim. Their bioactivities, including anticancer and antimicrobials, have been demonstrated in anti-growth, induction of apoptosis, and intermediate to G2-phase cell cycle (Aithal et al. 2009, 2011; Li et al. 2010). Juglones inhibit the intestinal carcinogenesis of mice treating with azoxymethane. They are hopefully chemo-defensive agents for intestinal neoplasia. Juglone shows to be possibly immune-stimulating for oncogenes (Polonik et al. 2003). Juglones have been activated synergistically by the cytotoxicity of the

etoposide process. The toxicity of juglone could not be ignored (Mathur et al. 2011; Seshadri et al. 2011). The anticancer activity of juglone could be attributed to the reduction of glutathione (GSH), induction of oxidative stress, and cell death through apoptosis and necrosis due to the harm of cell membranes (Fila et al. 2008; Ji et al. 2011). In addition, the inhibition of peptidyl-prolyl isomerase overexpresses in several cancer cells (Chao et al. 2001; Xu et al. 2012). Juglones suppress the activator protein-2α (AP-2α) and the epidermal growth factor receptor-2 (HER-2) promoter activity, the changing of B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated x protein (Bax), the activating of poly (ADP-ribose) polymerase (PARP), the release of cytochrome *c*, Smac, and apoptosis-inducing factor (AIF), and the induction of caspases activation (Fila et al. 2008; Ji et al. 2011; Khanal et al. 2010; Xu et al. 2010). Some analogs including 2,5-dihydroxy-3-(3-methylbut-2-enyl) naphthalene-1,4-dione and 2,3-dihydro-5-hydroxy-2-(prop-1-2-enyl) naphtho-[2,3-b]-furan-4,9-dione are most potential to anti-growth factors (Bonifazi et al. 2010).

### 14.6.4 β-Lapachone

A natural naphthoquinone, *β*-Lapachone, is isolated from *Tabebuia avellanedae* Lor. (Hussain et al. 2007). Their activities include anticancer, antimicrobials, and anti trypanocidal activities (Medeiros et al. 2010). *β*-lapachones activate selective death with a broad sense of cancers without eliminating unaffected tissues and anti-growth at the G1 transition (Li et al. 2003). Anticancer effects have been demonstrated in xenograft animals (; Dong et al. 2009). The *β*-lapachone constituent with radiotherapy has shown a potential treatment for agonist cancer (Suzuki et al. 2006). *β*-lapachone is utilized in monotherapy and other medicines (Miao et al. 2009). *β*-Lapachone activates topoisomerase II (Topo II) *α*-mediated DNA breaks instead of the Topo I-mediated DNA breaks. It inhibits the activity of Topo I contrary to camptothecin (Bentle et al. 2007; Frydman et al. 1997; Hori et al. 2011; Li et al. 1993). Therefore, *β*-lapachone inhibits DNA polymerase, the elicitation of endoplasmic reticulum stress, and induction of caspases activation (Lien et al. 2008). The increasing cytosolic Ca2+ is a vital mechanism for *β*-lapachone-induced apoptosis (Hori et al. 2011).

*β*-lapachone makes cells more sensitive to radiation through interrupting the contribution of quinone oxidoreductase (NQO1) in radiation-induced activation of NF-κB and inhibiting the repair of sublethal radiation damage (Bentle et al. 2007; Dong et al. 2010; Suzuki et al. 2006). However, *β*-lapachone has significant effects agonist antitumor; it was terminated as an antineoplastic in 1970 because of its toxicity (Almeida 2009).

### 14.6.5 Plumbagin

Plumbagins, an organic yellow dye, is isolated from *Plumbago* spp. L., and *Dyerophytum africanum* (Lam.) Kuntze. Their effects have been utilized in agonist

antioxidant, anticancer, anti-inflammatory, analgesic, and antimicrobial activities (Luo et al. 2010; Padhye et al. 2012). Plumbagins prevent prostate tumor, cancer angiogenesis, growth of carcinoma, and cancer growth (Lai et al. 2012; Li et al. 2012; Sand et al. 2012; Subramaniya et al. 2011; Sun and McKallip 2011). This effect can be seen in solid tumors and Ehrlich ascites model, melanoma, and hormone-refractory prostate cancer (Lai et al. 2012). Furthermore, plumbagin sponsors micronuclei induction (Aziz et al. 2008; Kumar et al. 2011a, b; Lai et al. 2012). Besides, plumbagin encourages cell cycle arrest at the G2/M phase (Gomathinayagam et al. 2008; Wang et al. 2008). This mechanism is due to their apoptosis, including intracellular ROS induction (Xu and Lu 2010), upregulation of p53, downregulation of cyclooxygenase-2 (COX-2), encouragement of caspases, and Bcl-2 family proteins (Kawiak et al. 2007; Li et al. 2012; Powolny and Singh 2008; Subramaniya et al. 2011; Sun and McKallip 2011; Tian et al. 2012; Xu et al. 2010).

Plumbagin inactivates the NF-κB pathway that suppresses NF-κB-regulated gene products, such as IAP, Bcl-2, Bcl-xL, survivin, cyclin D1, COX-2, and MMP-9 (Sandur et al. 2006). This constituent prevents the invasion and evolution of cancer by downregulating the expression of chemokine receptor CXCR4 by NF-κB inhibition (Manu et al. 2011). Furthermore, plumbagin has multidrug resistance related to ATP binding cassette drug transporter (Shukla et al. 2007). Other bioactivities inhibit mycobacterial development and reduce insect feed. (Dandawate et al. 2012; Mathew et al. 2010; Sreelatha et al. 2009).

### 14.6.6 Shikonin

Shikonins are isolated from the roots of *Lithospermum erythrorhizon* Sieb. et Zucc., which are utilized for burns, sore throats, measles, carbuncles, macular eruptions, and allergic disease (Wang et al. 2010). This bioactive constituent as a naphthoquinone pigment has anticancer, antioxidant, and anti-inflammatory activities (Wang et al. 2010; Yang et al. 2009). Anticancer activities involving the induction of apoptosis, delay of invasion, and antiproliferation have been in vivo determined in homograft and heterograft animal models (Yang et al. 2009). Anticancer mechanisms inactivate the NF-κB and upregulate p53 and p21, ROS generation. Others downregulate the CDKs and ER-α and activate caspases (Chang et al. 2010; Min et al. 2008; Min et al. 2011; Rao et al. 2011; Wu et al. 2012a, b; Yao and Zhou 2010). Also, this bioactive quinone prevents Topo II activity and damage DNA (Kretschmer et al. 2012; Yang et al. 2006). Shikonin is a chosen estrogen enzyme modulator expressing steroid sulfatase (STS) for estrogen biosynthesis (Zhang et al. 2009). As well, shikonin analogs may inhibit pyruvate kinase-M2 (Chen et al. 2011). Natural analogs evade drug resistance mediated by multiple drug resistance protein 1 and breast cancer resistance protein 1. They wield antiangiogenesis effect by the hang-up of vascular endothelial growth factor receptor 2 (Komi et al. 2009; Xuan and Hu 2009).

### 14.6.7 Thymoquinone

Thymoquinone is isolated from *Nigella sativa* L. This bioactive formulation belonging to benzoquinones has been vitally utilized for antioxidant, anti-inflammatory, and anticancer activities (Banerjee et al. 2009; Chehl et al. 2009; Sayed-Ahmed et al. 2010). The anticancer effects refer to diverse modes of action with the inducing of apoptosis, antiproliferation, antiangiogenesis, anti-metastasis, and cell cycle seizure (Banerjee et al. 2009; El-Mahdy et al. 2005; El-Najjar et al. 2010; Kolli-Bouhafs et al. 2011). The antitumor was examined in xenograft mice models for tumors of prostate, pancreatic, and colon (Banerjee et al. 2009; Gali-Muhtasib et al. 2008; Jafri et al. 2010; Kaseb et al. 2007). Thymoquinone prevents doxorubicin-resistant human breast cancer MCF-7/DOX cell proliferation deprived of unveiling cytotoxicity to normal human colonic FHs74Int cells (Arafa et al. 2011; El-Najjar et al. 2010). Thymoquinone with orthodox chemotherapeutic medicines, including cisplatin, gemcitabine, 5-fluorouracil, doxorubicin, and oxaliplatin, affect various cancer families (Banerjee et al. 2009; Jafri et al. 2010; Lei et al. 2012; Woo et al. 2011). Doses of toxic thymoquinone make the effusion of lymphoma cells more sensitive to the TNF-related apoptosis-induced ligand. It is due to the upregulation of the death receptor-5 (Hussain et al. 2011).

The anticancer activity effect takes place via the modification of numerous molecular targets, for instance, NF-κB, p73, AKT, tubulin, peroxisome proliferator-activated receptor γ (PPARγ), the signal transducer and activator of transcription 3 (STAT3), phosphatase and tensin homolog (PTEN), polo-like kinase-1 (PLK1), androgen receptor (AR), E2F-1, Bcl-2, FAK, and MMPs (Alhosin et al. 2010; 2012; Arafa et al. 2011; Badr et al. 2011a, b; Banerjee et al. 2009; Hussain et al. 2011; Kaseb et al. 2007; Kolli-Bouhafs et al. 2011; Reindl et al. 2008; Sethi et al. 2008; Woo et al. 2011). Thymoquinone produces ROS. Thymoquinone damages DNA and inhibits telomerase activity (El-Najjar et al. 2010; Gurung et al. 2010; Hussain et al. 2011). Treatment by thymoquinone stops CXCL12-mediated chemotaxis in myeloma cells and lowers CXCR4 expression and CXCL12-mediated CXCR4/CD45 association (Badr et al. 2011a, b). Numerous analogs of thymoquinone are manufactured utilizing modulations at the benzenoid or carbonyl spots. Some formulations are more effective than thymoquinone and affect antiproliferation in human pancreatic cancers (Banerjee et al. 2010). The 6-hencosahexaenyl conjugate is an effective antiproliferative of 518A2 melanoma, HL-60 leukemia, KB-V1/Vbl cervix carcinoma, and MCF-7/Topo breast adenocarcinoma cells (Breyer et al. 2009).

## 14.7 Commercial Utilization and Prospects

Quinones are utilized and served in various capacities. They manufactured dye fabrics (red-violet) and used them to transport energy and hydrogen atoms (Coenzyme Q10). Therefore, they provide essential nutrients (Vitamin K) and serve as

cocatalysts (PQQ). In the pharmaceutical industry, quinones eradicate cancer (doxorubicin), HIV (streptonigrin, STN), and bacteria (prekinamycin).

Previous pharmacologic studies stated promising activities, including antipruritic, anti-dermatitic, antihistaminic, antimicrobial (bacteria and fungi), analgesic, antioxidant, anti-inflammatory, antirheumatic, anti-anaphylactic, antitumor, and anticancer activities. Various extracts are often associated with an existence of natural constituents, including quinones, glycosides, alkaloids, flavonoids/flavanols, anthocyanins, saponins, phenolics, and terpenoids.

Orobanchaceae plants' parasitizing roots that reason extensive losses in agroproduction worldwide advance haustoria in the existence of the DMBQ. The host-derived quinone compound DMBQ is an effective haustorium-inducing factor in various Orobanchaceae species. The molecular processes that are basis of conception and go in advance of the formation of the haustorium are unclear. The DMBQ signaling components identification is challenging in parasitic plants, as key research tools, for instance, trans-generational genetic changes are unavailable. Understanding plant quinone identifying and the molecular proceedings that track DMBQ conception would sense a better comprehend of signaling and offer a molecular target to contest parasitic plants. This offers insights into the role of quinone signaling. Perception of CARD1 function helps to better realize the signaling pathways during the haustorium formation in parasitic plants and the immunity events in nonparasitic plants.

## 14.8 Conclusions and Recommendations

The importance of commercial and societal demand makes the scientific-gate always require more efforts towards biosynthesis pathway and its scale-ups of natural products. However, evident efforts on in vitro production are obviously from new works. Progression of plant biotechnology helps obviously to be utilized in various directions: (1) biodiversity conservation. The demand for raw materials of tissues, (2) alternative means. It offers numerous new strategies to justify industrial calls, (3) eating-up the time. The high and fast yield of metabolite products may reduce the time, (4) biosynthesis pathway. Help to sense well the complex pathways of biometabolites, (5) physiological and genetic correlation. Well, understand the relation between bearers of metabolic engineering and suppression/overexpression genes. (6) chemotaxonomic marker.

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