and punicalin (**10**) from *Terminalia* species exhibited inhibitory effects on hepatotoxicity induced by acetaminophen [75] and $CCl_4$ [38]. Other activities associated with the antioxidative effects of punicalagin (**9**) include the suppression of bleomycin-induced genotoxicity in cultured Chinese hamster ovary cells [76] and of the proliferation of H-ras-transformed NIH3T3 cells. These effects are due, in part, to decreases in intracellular superoxide levels, which may modulate downstream signaling of Ras protein [77].

### *5.3. Lagerstroemin* (**29**)

*Lagerstroemia speciosa* (Lythraceae) has been used as an herbal medicine for the treatment of diabetes in the Philippines. Screening of the plant extract identified lagerstroemin (**29**), flosin B ($C_1$-epimer of **29**), and reginin A (**49**) as activators of glucose transport using rat fat cells, all of which are characteristic *C*-glycosidic ellagitannins of the plant [78]. The insulin-like activity of **29** was indicated by increases in glucose uptake by rat adipocytes, and by increased tyrosine-phosphorylation in Chinese hamster ovary cells expressing human insulin receptors [79]. In addition, casuarinin (**20**), stachyurin (**21**), and casuariin (**22**) as well as **29** were identified as active components in the stimulation of insulin-like glucose uptake and in the inhibition of adipocyte differentiation (**20** and **29**) in 3T3-L1 cells [80].

### *5.4. Oenothein B* (**54**) *and Related Macrocyclic Oligomers*

Macrocyclic oenothin B (**54**) reportedly exhibited remarkable host-mediated antitumor activity with intraperitoneal injection several days before inoculation of sarcoma 180 tumor cells into the abdomen of mice [24]. Evaluation of activity was gauged by the number of survivors and the percent increase in life span (%ILS) 60 days after administration. Treatment with a 10 mg/kg dose of oenothein B (**54**) resulted in 4 survivors out of 6 mice and 196% ILS, the most potent results of among the approximately 100 polyphenols evaluated. This activity was related to an immunomodulatory effect consisting of macrophage activation and consequent release of cytokine interleukin-1β [87]. Woodfordin C (**53**) also exhibited a potent activity with 160% ILS and one survivor out of five mice after 60 days [56]. The potent activity of the oligomeric ellagitannins stands in contrast to the negligible activity observed with most of the monomeric hydrolysable tannins, proanthocyanidins, and related low-molecular weight polyphenols.

Woodfruticosin (woodfordin C) (**53**) was also an effective inhibitor ($IC_{50}$ 2.5 μg/mL) of deoxyribonucleic acid topoisomerase II, the potency of which was 10-fold stronger than that of adriamycin and etoposide in molar concentrations [81].

Eugeniflorin $D_1$ and $D_2$ (**57**) as well as oenothein B (**54**) obtained from the extract of *Eugenia uniflora* (Myrtaceae) were efficient inhibitors of Epstein-Barr virus (EBV) DNA polymerase, a key enzyme for replication of EBV associated with nasopharyngeal carcinoma [82].

Using activity-guided fractionation for bioactive components of *Epilobium* species, Ducrey *et al.* [59] showed that oenothein A (**59**) and B (**54**) are potent inhibitors of 5α-reductase and aromatase, which are involved in the etiology of benign prostatic hyperplasia.

Biological studies of an oenothein B analog, cuphiin $D_1$ (**55**), isolated from *Cuphea hyssopifolia* (Lythraceae) revealed antitumor effects through the induction of apoptosis in human promyelocytic leukemia (HL-60) cells and human cervical carcinoma (HeLa) cells [85]. Cuphiin $D_1$ (**55**) was also shown to activate human peripheral blood mononuclear cells to release cytokines IL-1β, IL-2 and TNF-α [84].

Many pathogenic bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), have acquired resistance to various clinical antibiotics. This worldwide problem is driving the development of new antibiotic drugs. Observed synergistic effects of certain polyphenols such as oenothein B (**54**) and tellimagrandin I (**1**) have been suggested as a means to restore the effectiveness of β-lactam antibiotics against MRSA. When used together with these tannins, the MICs of oxacillin against MRSA strains were markedly lowered to 1/250 or 1/500 [88]. These results may represent one strategy for overcoming emergent bacterial resistance.

### *5.5. Nobotanins*

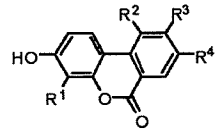
In a survey for new, natural anticancer chemotherapeutic drugs, some oligomeric ellagitannins showed promise as inhibitors of poly(ADP-ribose) glycohydrolase, which is associated with gene activation upon DNA repair, replication, and transcription [86]. During initiation of gene expression, DNA replication, and cell differentiation, poly(ADP-ribose) from specific chromosomal proteins is degraded primarily by poly(ADP-ribose) glycohydrolase to yield ADP-ribose and mono(ADP-ribosyl) proteins. It has been suggested that this degradation of poly(ADP-ribose) is an important factor in the regulation of gene activation. Ellagitannins showed an appreciable inhibitory effect with an $IC_{50}$ of 0.3–11.9 μM on poly(ADP-ribose) glycohydrolase purified from human placenta. Procyanidin oligomers and their constituent flavan-3-ols were inactive even at concentrations of 100 μM. Potent activity was exhibited by oligomeric ellagitannins, including dimers such as oenothein B (**54**) ($IC_{50}$ 4.8 μM) and nobotanin B (**70**) ($IC_{50}$ 4.4 μM), a trimer (nobotanin E (**73**), $IC_{50}$ 1.8 μM), and a tetramer (nobotanin K (**72**), $IC_{50}$ 0.3 μM).

## 6. Conclusions

A large number of ellagitannins have been isolated and characterized from a wide array of plant sources during the last several decades. The plants from which individual ellagitannins were first isolated belonged largely to the order Myrtales. Most notably, several *Terminalia* species of Combretaceae produce punicalagin and its congeners, all of which contain a unique gallagyl group, previously found only in *Punica granatum* (Punicacease). These findings imply a close chemotaxonomic relationship between these plants. Approximately 40% of the oligomeric ellagitannins characterized thus far were initially isolated from species of Onagraceae, Lythraceae, Myrtaceae, Trapaceae, and Melastomataceae, indicating that these plant varieties are good natural sources of these oligomers. In particular, macrocyclic tannins, which include oenothein B and its analogs, are characteristic of the Onagraceae, Lythraceae, and Myrtaceae. Various *in vitro* and *in vivo* assays have demonstrated diverse biological activities for these ellagitannins and indicate the potential of these materials as antioxidant food additives [89]. However, although there are several reports that

identify ellagitannin metabolites in animal urine and feces, e.g., ellagic acid derivatives (**77**, **78**) [90] and compounds **79–84** [91], the bioavailability of these tannins in humans has not been studied extensively.

**Figure 14.** Structures of metabolites from ellagitannins.




**77**: $R^1$= $R^2$= $R^3$= H, $R^4$= OH
**78**: $R^1$= $R^2$= $R^3$= $R^4$= H
**79**: $R^1$= $R^2$= H, $R^3$= OMe, $R^4$= OH
**80**: $R^1$= $R^2$= H, $R^3$= OH, $R^4$= OMe
**81**: $R^1$= $R^2$= H, $R^3$= $R^4$= OH
**82**: $R^1$= $R^2$= $R^3$= $R^4$= OH
**83**: $R^1$= H, $R^2$= $R^3$= $R^4$= OH
**84**: $R^1$= $R^3$= H, $R^2$= $R^4$= OH

Further studies in this field will include characterization of immunomodulating effects in the digestive tract that could clarify the role(s) of ellagitannins in human health and help explain their widespread use in traditional medicines.

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