



## Technical White Paper

### **Biodegradable Polymers from Functionalized Phenolics**

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**Abstract:** *This white paper is intended to provide the readers with an overview of novel functionalized phenolic monomers and absorbable polymers there from, developed by our company. Phenolics are an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and agrochemical applications. This is attributed to their anti-oxidative, anti-inflammatory, anti-mutagenic, anti-carcinogenic properties coupled with their capacity to modulate key cellular enzyme function. Hence, motivation to develop absorbable polymers with tunable hydrolytic degradation profiles that incorporate phenolic compounds in the polymer backbone, and which upon degradation under physiological conditions yield safe and biocompatible products formed the basis of this work. This will not only add therapeutic value to these polymers, but will also enable these polymers to deliver phenolics at the site of action in a controlled manner. In order to meet these objectives, a variety of phenolics including drugs, natural products, amino acids and neurotransmitters were functionalized with safe and biocompatible glycolic acid, lactic acid, p-dioxanone and caprolactone monomers. These monomers are building blocks of majority of biodegradable polymers used to make commercial medical devices. The resulting functionalized phenolic monomers were then polymerized to yield absorbable therapeutic polymers. Furthermore, these absorbable polymers will find use in a number of biomedical applications including controlled drug delivery, tissue adhesive and sealants, coatings and radiation stable medical devices among numerous others.*

#### **1.0 Phenolics: Importance and Applications**

Phenolics or phenolic compounds are defined chemically as substances that have one or more aromatic rings and bear one or more hydroxyl substituent(s) attached directly to the ring. They occur widely in nature and are universally distributed throughout the plant kingdom in seeds, plant oils, vegetables, tea, coffee and a number of herbal compounds including Gingko biloba, ginseng, ginger and Hawthorne. Phenolics encompass a wide variety of compounds including the following:

- **Polyphenols** such as flavonoids and tannins. Flavonoids are very useful in alleviating conditions related to chronic venous insufficiency including thrombosis, hemorrhoids and eye problems including macular degeneration. In addition, they are also helpful in treatment of tendonitis, rheumatoid arthritis, joint injury, fibromyalgia, cellulite, and gout.
- **Amino acids** such as tyrosine



- **Neurotransmitters** such as Serotonin, Dopamine and Adrenaline. L-DOPA, the precursor of Dopamine is used in the treatment of Parkinson's disease.
- **Phenolic Acids** such as Caffeic acid, Ferulic acid and p-Coumaric acid found in coffee
- **Essential oils** such as Eugenol and Methyl Salicylate found in clove oil and oil of wintergreen respectively.
- **Drugs** containing phenolics and functionalized phenolic groups such as Aspirin, Paracetamol, Naproxen, Capsaicin, Phenacetin and Chloroxylonol.
- **Natural Phenolics** such as Vanillin, Diadzein, Coumarins, Isopimpinellin and Resveratrol

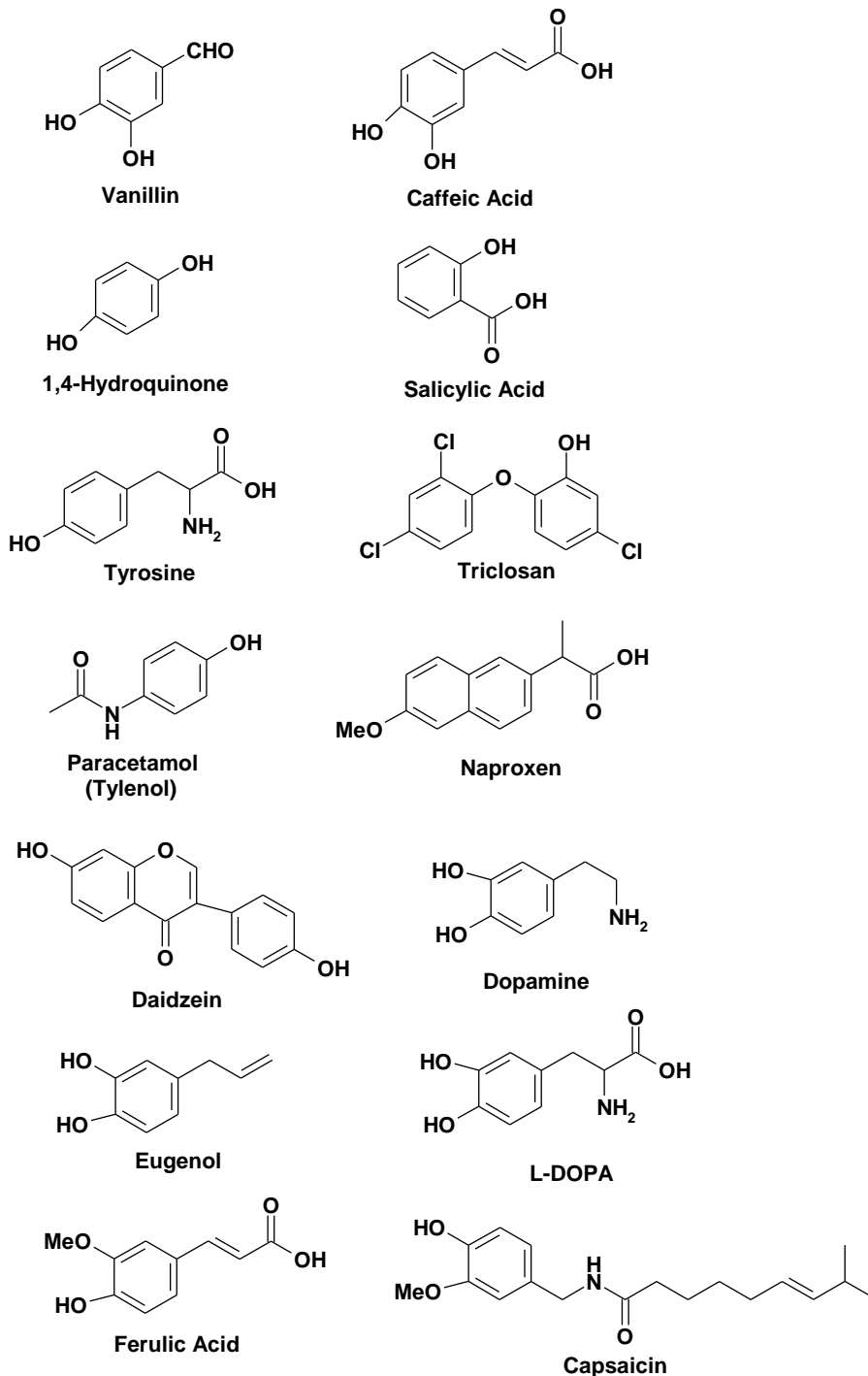
The structures of some of these phenolics are shown in *Figure 1*. Beneficial attributes of phenolics stem from their anti-oxidative, anti-inflammatory, anti-mutagenic, anti-carcinogenic properties coupled with their capacity to modulate key cellular enzyme function. These attributes enable phenolics to play a key role in the growth and reproduction of plants while serving as anti-feedants and anti-pathogens. Furthermore, phenolics based plant pigment products function as antibiotics, natural pesticides, signal substances for the establishment of symbiosis with rhizobia, attractants for pollinators, protective agents against ultraviolet light, insulating materials to make cell walls impermeable to gas and water, and as structural materials to give plants stability. Moreover, phenolic compounds also aid in the maintenance of food, fresh flavor, taste, color, and prevention of oxidation deterioration. It is by virtue of these properties that phenolics are an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and agrochemical applications. Hence, most of the phenolics are considered to be safe and biocompatible.

In spite of the availability and numerous uses of phenolics, some of their biomedical applications are limited by their insolubility in water under physiological conditions. Furthermore, they can also be very difficult to polymerize in the phenolic state. Hence, it is desirable to enhance their native value by, for example, providing phenolics or combinations of phenolics with a specific controlled degradation profile or range enabling controlled release of the phenolic over an extended, controllable time range under physiological conditions while retaining their inherent biological activity.

## **2.0 Functionalized phenolic monomers and biodegradable polymers therefrom**

In order to overcome the previous limitations and drawbacks of phenolics as described in *section 1.0* above which restricts their biomedical applications, and to enhance the native value of phenolics while retaining their biological properties, we at Bezwada Biomedical, LLC have developed novel functionalized phenolic monomers. These functionalized phenolic monomers are prepared by functionalization of phenolic group(s) with hydroxy acids such as glycolic acid, lactic acid, open chain caprolactone and open chain p-dioxanone via either esterification, etherification or amidation as shown in *Scheme 1*. These hydroxy acids are the base materials of absorbable and biocompatible polymers and copolymers such as poly (lactide) (PLA), poly(glycolide) (PGA), poly(caprolactone) (PCL), poly(p-dioxanone) (PDS), poly(lactide-co-glycolide) and poly(glycolide-co-

caprolactone), the key components of majority of absorbable medical devices ranging from sutures, staples, orthopedic screws and implantable surgical devices to tissue



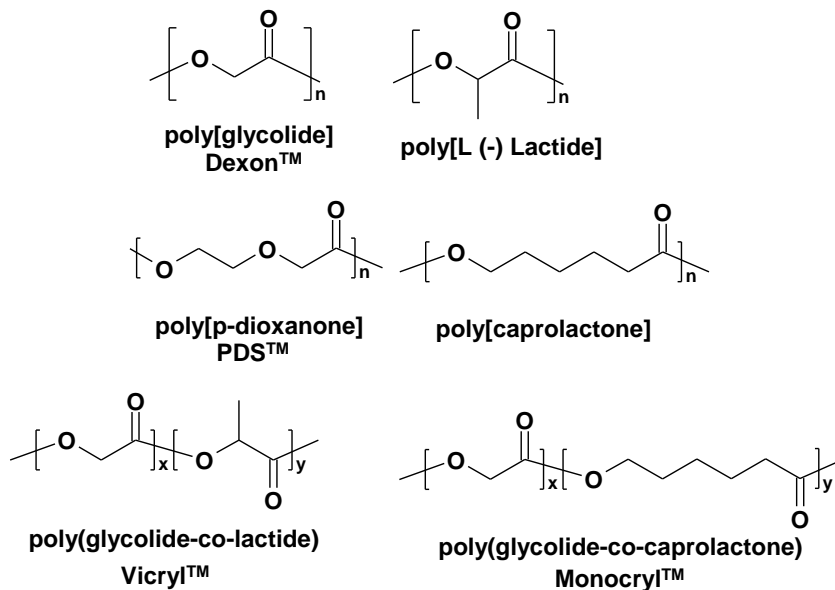
**Figure 1** Structures of some selected phenolics



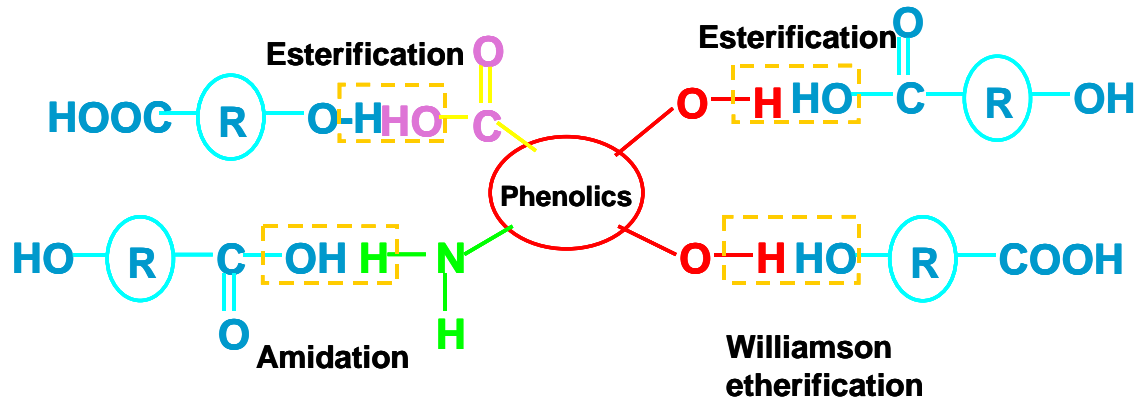
engineering scaffolds. *Figure 2* depicts the structures of these polymers and copolymers. These polymers have the advantage of being readily hydrolyzed into their constituents such as lactic acid, glycolic acid and hydroxyhexanoic acid that are eliminated by the usual metabolic pathways and hence considered to be safe and biocompatible polymers.

Functionalization enhances the native value of the phenolic compound. For instance, functionalization via esterification results in phenolic monomers, which upon hydrolysis release the phenolic in its native form. Furthermore, these functionalized phenolic monomers can be designed to degrade at a controlled rate under physiological conditions. Moreover, all these functionalized phenolic monomers are precursors for the absorbable polymers that have the following attributes

- incorporates phenolic compounds in the polymer backbone
- degrades into safe and biocompatible products upon hydrolysis under physiological conditions
- deliver therapeutic values of phenolics at the site of action in a controlled manner
- tunable hydrolytic degradation profile



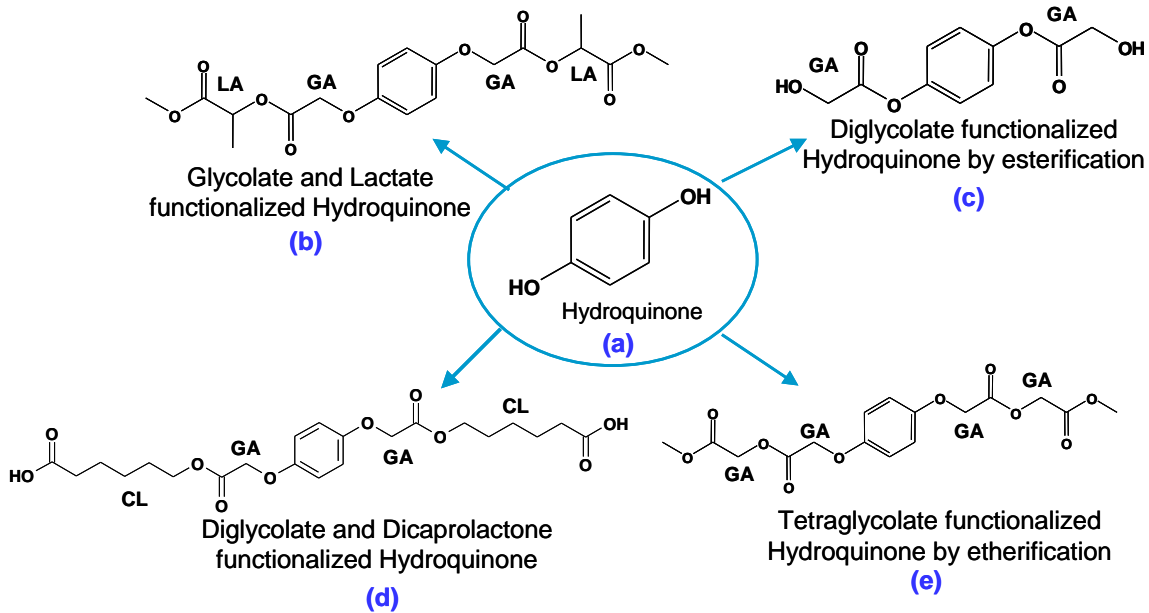
**Figure 2** Absorbable polymers and copolymers



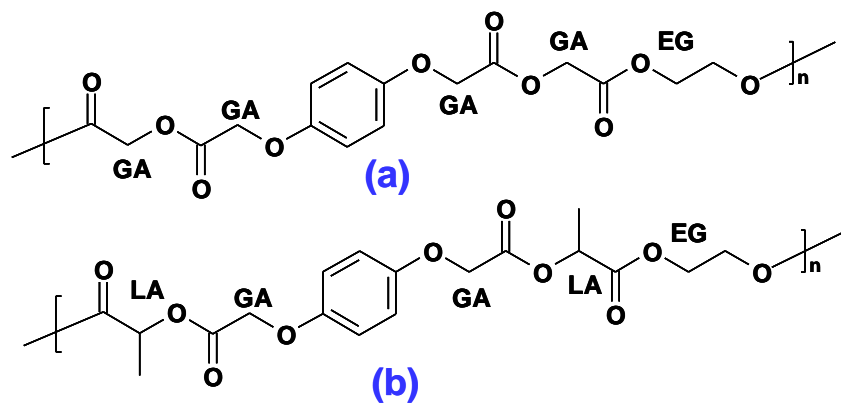
**Where R= backbone of glycolic acid or lactic acid  
or Caprolactone or p-dioxanone**

**Scheme 1** Functionalization of phenolics with safe and biocompatible molecules

The following section depicts the structures of some functionalized phenolic monomers and absorbable polymers derived from them with tunable hydrolytic degradation profiles. For instance, *figure 3* and *figure 4* depict the structures of functionalized hydroquinone monomers and radiation stable absorbable polymers derived from them, respectively, wherein both the monomers as well as polymers have controlled degradation rates. Glycolic acid functionalized hydroquinone monomers and corresponding polymers will hydrolyze faster than lactic acid and caprolactone functionalized monomers and corresponding absorbable polymers. Furthermore, using different combinations of functionalization moieties enables us to control the hydrolytic degradation rates of monomers and polymers. The absorbable polymers derived from hydroquinone can be used to prepare radiation stable absorbable sutures and coatings for implantable devices. In addition, these radiation stable polymers can be very useful for controlled release of injectable drugs as well as in tissue engineering applications.

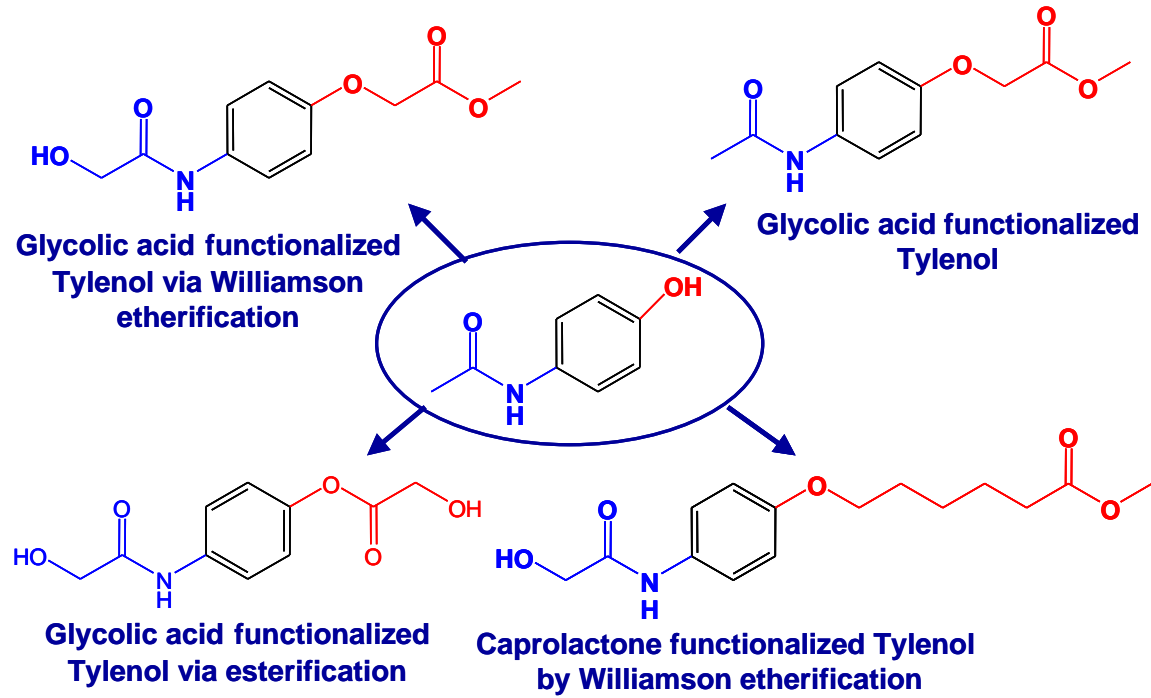


**Figure 3** Functionalized Hydroquinone monomers (a) Hydroquinone (b) Hydroquinone diglycolate dilactate (c) Hydroquinone diglycolate (d) Hydroquinone diglycolate dicaprolactone and (e) Hydroquinone tetraglycolate where GA is Glycolic acid, LA is Lactic acid and CL symbolizes Caprolactone unit

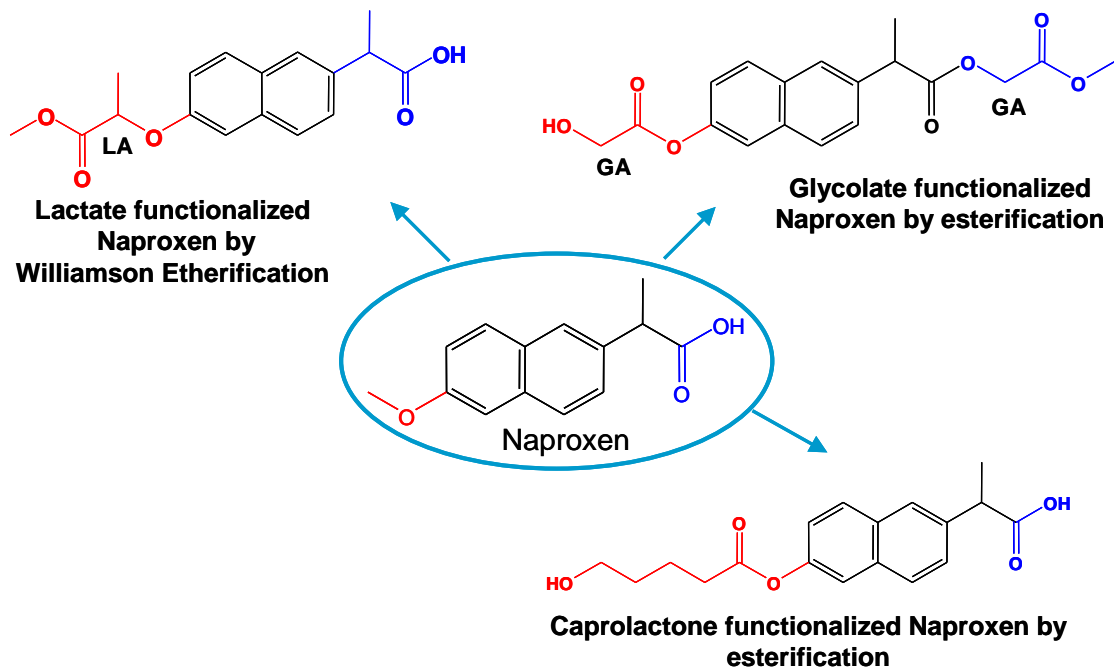


**Figure 4** Absorbable polymers derived from (a) Hydroquinone tetraglycolate and (b) Hydroquinone diglycolate dilactate

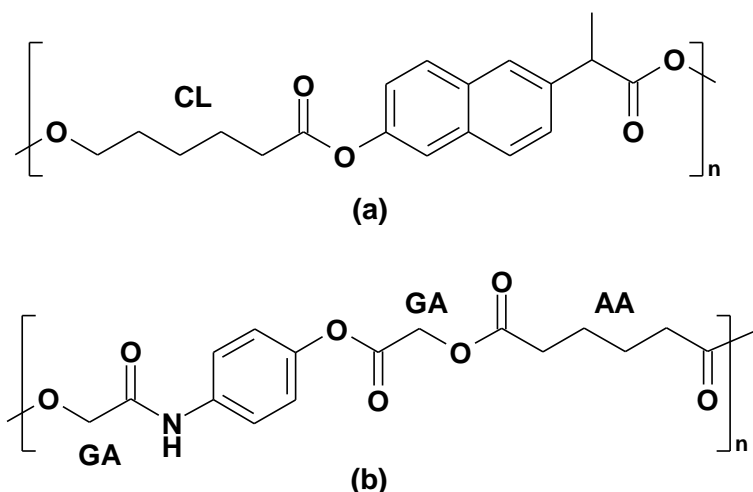
**Phenolic Drugs:** Figures 5 and 6 depict the structures of functionalized Tylenol and Naproxen monomers. These *phenolics* fall under the category of *drugs*.



**Figure 5** Functionalized Tylenol monomers



**Figure 6** Functionalized Naproxen monomers



**Figure 7** Absorbable polymer derived from (a) functionalized Naproxen monomer and (b) functionalized Tylenol monomer where GA is Glycolic acid, CL is Caprolactone and AA symbolizes Adipic acid unit

These absorbable polymers not only have a controlled hydrolytic degradation profiles but are also anticipated to degrade into safe and biocompatible molecules while retaining the inherent biological activity of Naproxen and Tylenol respectively.

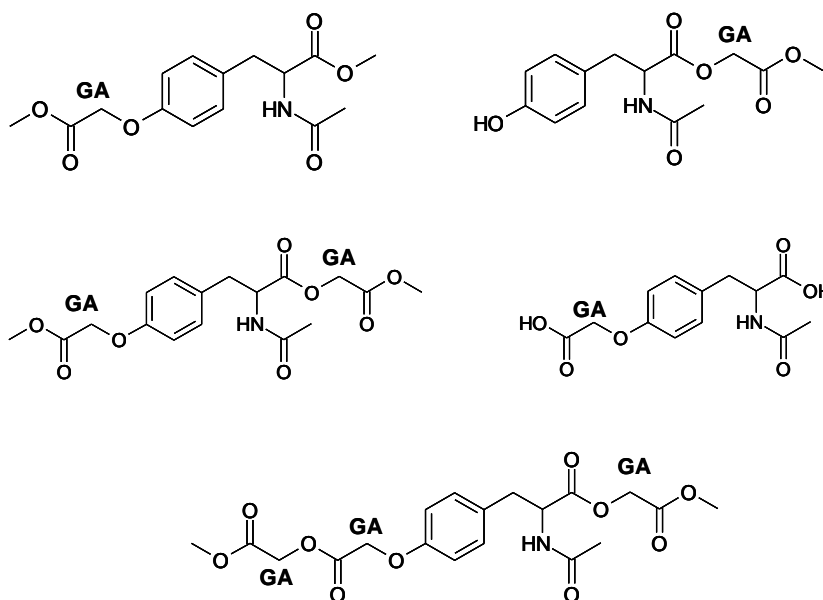
**Phenolic Amino acid:** In another example, we have also prepared functionalized *tyrosine* monomers and have developed absorbable polymers from them. Tyrosine is a non-essential *phenolic* amino acid. It is a parent amino acid for skin, hair and eye pigments. Furthermore, it is an important precursor for neurotransmitters epinephrine, nor epinephrine and dopamine and hence plays an important role in transmission of nerve impulses to the brain; helps overcome depression; improves memory; increases mental alertness; and promotes the healthy functioning of the thyroid, adrenal, and pituitary glands. Such attractive properties of tyrosine led many research groups to develop absorbable polymers from tyrosine. However, tyrosine derived polymers developed and studied so far have either very slow or incomplete biodegradation or have marginal engineering properties. These have been the major obstacles for the practical applications of these polymers for biomedical applications. This necessitates the need to develop novel biocompatible and absorbable tyrosine based polymers with combined attributes of excellent engineering properties, improved efficacy and tunable hydrolysis profile.

Tyrosine contains a phenolic, carboxylic acid and an amine group. In the present study, either of these functional groups in tyrosine was functionalized with glycolic acid, lactic acid and caprolactone moiety as shown in *figure 8*. This functionalization resulted in the formation of novel functionalized tyrosine monomers which were then either self condensed or condensed with ethylene glycol to yield novel absorbable polymers containing tyrosine in the polymer backbone as shown in *figure 9*. These absorbable polymers not only have excellent engineering properties, improved efficacy and

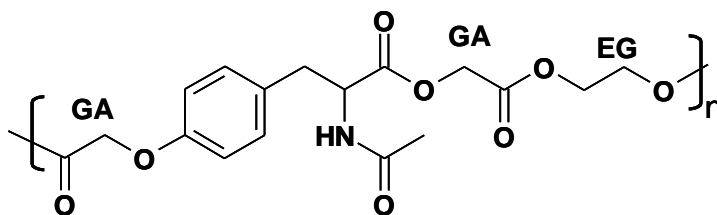




controlled hydrolytic degradation profiles but are also anticipated to degrade into safe and biocompatible molecules while retaining the inherent biological activity of tyrosine.

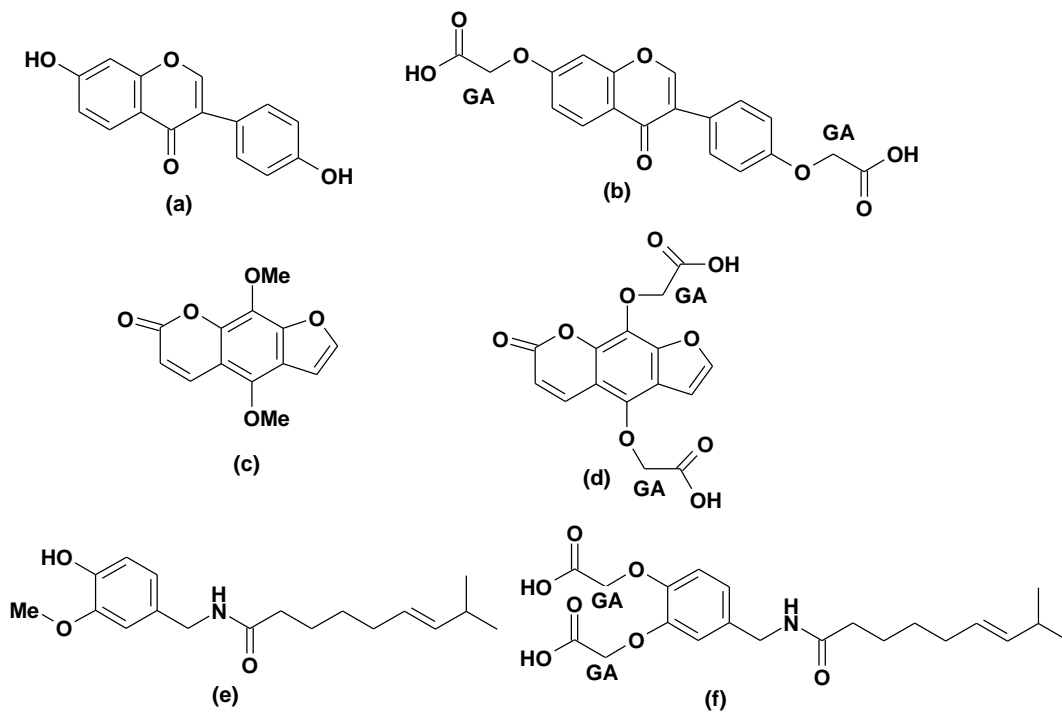


**Figure 8** Functionalized Tyrosine monomers where GA symbolizes Glycolic acid

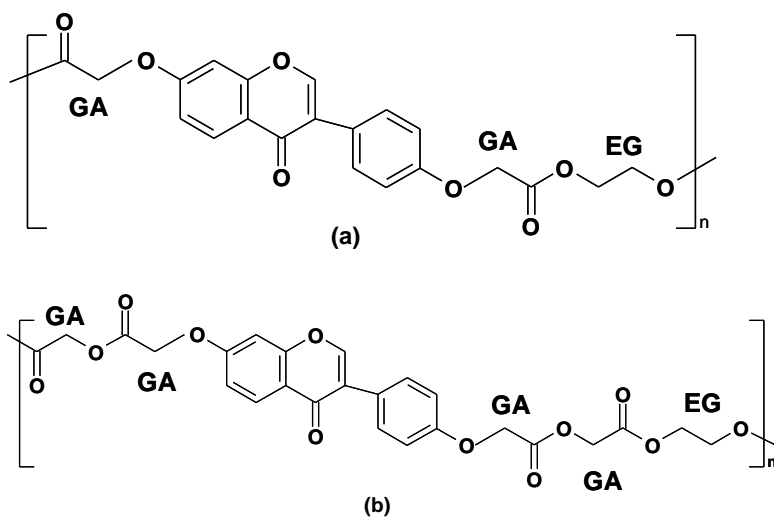


**Figure 9** Absorbable polymer from functionalized Tyrosine monomer where GA symbolizes Glycolic acid and EG symbolizes Ethylene glycol

**Phenolic Natural Products:** At Bezwada Biomedical, we have also developed novel absorbable polymers from functionalized natural products in order to incorporate the therapeutic values inherent to the natural products in the polymer backbone. For instance, natural molecules belonging to three different classes of natural products i.e. Daidzein (Isoflavone with antioxidant and hormonal activity), Isopimpinellin (Coumarin with anticancer properties) and Capsaicin, an alkaloid with analgesic properties used in topical ointments were functionalized with safe and biocompatible molecules such as glycolic acid, lactic acid, p-dioxanone and caprolactone as shown in *figure 10*. The resulting novel functionalized natural product monomers were then polymerized by condensation with diols to yield absorbable therapeutic polymers. For example, *figure 11* depicts structures of specific examples of absorbable polymers derived from functionalized Daidzein molecule.



**Figure 10.** (a) Daidzein (b) Glycolic acid functionalized Daidzein (c) Isopimpinellin (d) Glycolic acid functionalized isopimpinellin (e) Capsaicin (f) Glycolic acid functionalized Capsaicin

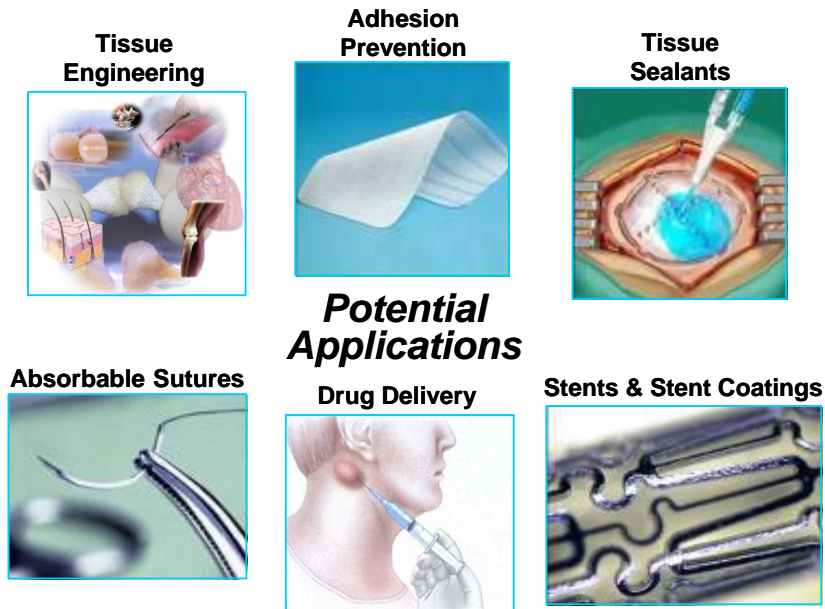


**Figure 11 (a)-(b)** Absorbable polymer from glycolic acid functionalized Daidzein and ethylene glycol with different hydrolytic degradation rates.



### ***3.0 Potential biomedical applications of absorbable polymers derived from novel functionalized phenolic monomers from Bezwada Biomedical***

- Tissue adhesives and sealants
- Adhesion prevention barrier
- Absorbable scaffolds for tissue engineering
- Absorbable coatings
- Radiation stable medical devices
- Controlled drug delivery



**Summary:** In summary,

- At Bezwada Biomedical, we have developed novel functionalized phenolic monomers as well as biodegradable polymers from these monomers.
- The resulting polymers incorporate biological values inherent to the phenolics in the polymer backbone. Furthermore, they have tunable hydrolytic degradation profiles, wherein the hydrolytic degradation rate of these absorbable polymers is controlled by varying the chain length of the degradable linkage and by varying the safe and biocompatible molecule within the degradable linkage i.e. replacing glycolide with lactide or p-dioxanone etc. Moreover, these absorbable polymers derived are anticipated to degrade into safe and biocompatible molecules under physiological conditions and deliver phenolics at the site of action in a controlled manner.
- Both the functionalized phenolics as well as the absorbable polymers derived from them are anticipated to have numerous biomedical applications.



Think Absorbable. Think Bezwada Biomedical

*For further information on how we can help you engineer your success, please contact us at [rao@bezwadabiomedical.com](mailto:rao@bezwadabiomedical.com) or visit us at [www.bezwadabiomedical.com](http://www.bezwadabiomedical.com)*

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