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Modification of condensed tannins: from polyphenol chemistry to materials engineering

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Condensed tannins (CT) are high molar mass polyphenolic bio-polymers based on flavonol units. CTs have been well-studied as due to their respective biological activity. However, the application of CTs in several areas is limited because of their physicochemical properties. The objective of this review is to investigate the state of the art regarding the chemical modification of CTs, and to outline recent and potential applications of tannin derivatives. An overview on the most important reactions is given, and a comprehensive summary of the experimental parameters for modification (chemicals, time, temperature, solvent type, and yield) is presented. The impact of the modification on the physicochemical properties of derivatives in comparison to native tannin behavior is discussed. Finally, the applicability of modified or unmodified CTs is described, referring to academic articles and patents. Future research in terms of modification reaction type, as well as derivatizing agents, is discussed.

1. Condensed tannin (CTs): renewable building-blocks polymers

1.1. CT as abundant polyphenols

Metabolites produced by living organisms are classified as either primary or secondary. Primary metabolites are essential, and their concentration within the organism depends only on it´s physiological state.[1] Proteins, nucleic acids, carbohydrates, and lipids are prominent examples for primary metabolic products. In contrast, secondary metabolites are not strictly essential for the survival of the organism, but they play an important ecological role in nature.[2] There are five major classes of secondary metabolites defined by their chemical structure: Nitrogen compounds (alkaloids, non-proteinogenic aminoacids, lectins, and cyanogens), isoprenoids (terpenes and steroids), polyketides, fatty acids, and phenols are the main groups found in nature.[3]

Phenolic structures with more than one -OH group, which are called polyphenols, are the largest class of secondary metabolites in vascular plants and they are mainly constituted from phenyl propanoids (coumarins, flavonoids, tannins, and lignin) from the Shikimate-Cinnamate pathway.[4] Polyphenols are synthesized exclusively in vascular plants and in a wide variety of species (*e.g.* monocotyledons, dicotyledons, ferns, and conifers), and plant tissues (*e.g.* leave, cone, seedpot, wood, blade, stipe, and bark).[5] However, this review will focus on CTs as the most studied polyphenols nowadays.

In vascular plants, tannins are the third most abundant group of secondary metabolites after the two main wood constituent carbohydrates (in the form of cellulose and hemicellulose) and lignin. Despite that lignin is the widest distributed aromatic biopolymer in nature, the peculiar reactivity, diverse biological activity, high -OH/monomer content, and versatility of CTs in term of physicochemical properties are recognized advantages for developing CTs-based biomaterials. In addition, soft tissues of woody plants such as leaves, needles, and bark, tannins can exceed lignin in abundance.[5]

Tannins are divided in two different classes: hydrolizable tannins (HT) and CTs. The former were found in chestnut (*Castanea* sp.), myrobolans (*Terminalia* and *Phyllantus* sp.), dividivi (*Caesalpinia* sp.), oak (*Quercus* sp.), eucalyptus (*Eucalyptus* sp.), and extracts of asian *Myrica* sp. The limited distribution of HTs comprising only some dicotyledonian species, as well as their molecular structure and their low nucleophilicity decreased the interest in their utilization beyond traditional uses.[7] CTs constitute more than 90% of the total world production of commercial tannins (>350.000 tons/year), and are chemically and economically more interesting as bio-polymer.[6,7] CTs and their flavonoid precursors are substantially concentrated in some barks and woods. They are highly abundant in barks of legumes (*Acacia* sp. (wattle or mimosa), *Lotus* sp., and *Sericea* sp.), conifers (*Tsuga* sp. and *Pinus* sp.), birch (*Betula* sp.), gambier (*Uncaria*

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sp.), and mangrove (*Rhizophora* sp.) species, and in the wood of *Schinopsis* sp. (Quebracho). Tannin extracts mainly from barks of *Pinus pinaster* or *Acacia* sp.[2-4], and from *Schinopsis* sp. wood are commercially exploited. The main use of CTs comprise alternative medicine, leather industry, and for adhesives preparation. Table 1 shows the CT content of selected tanniferous species.

Table 1. CT bark content of tropical and subtropical woody plants.

Species	Extractives (%)	CTs (%)	Ref.
Larix leptolepis	2.9-11.0	41.8-55.6	3
Rhizophora apiculata	12.8-20.2	43.5-50.8	
Acacia mangium	18.4-37.9	46.7-52.9	
Acacia auriculiformis	18.9-28.6	38.1-52.6	
Acacia nilotica	49.5-55.0	11.5-13.0	5
*Schinopsis balansae**	23.0	21.0	6
Pinus radiata	16.0-20.0	12.0-16.0	
Acacia mearnsii	42.0-51.0	35.0	
Rhizophora mangle	45.0	36.0	
Pinus pinaster	35.8-50.0	15-25	7
Pinus caribaea	17.6	9.2-15.4	9
Picea abies	33.0	8.0-11.0	11

*from wood

1.2. CT chemistry

The monomer unit of CTs consist of flavonoid units (C_{15}: flavan-3-*ols* or flavan-3,4-*diols*), which are condensed by 4→8 or 4→6 linkages. Their structure is a derivative of the basic C_6-C_3-C_6 flavan unit, being two aromatic rings separated by three carbon atoms.[12,13] The flavan rings are labelled A, C, and B, respectively, with a systematic numbering of carbon atoms (Fig. 1).

The CT chemistry is dominated by the presence of multiple -OH groups with narrowly but varying dissociation constants (*p*Ka catechin-base CTs: *p*KaC-3´-OH: 9.02; *p*KaC-4´-OH: 9.12; *p*KaC-5-OH: 9.43; *p*KaC-7-OH: 9.58). In consequence, acid and base catalyzed rearrangements, nucleophilic substitutions, and electrophilic aromatic substitutions are common reactions.[14,15]

Nucleophilic substitution occurs at the –OH, introducing either acyl- or alkyl- groups. Acylation is commonly achieved by reaction with acid chlorides or anhydrides[16], whereas alkylation is achieved with alkyl halides or epoxides.[15] These reactions are the focus of this review and are described in detail in the sections below.

Activation towards electrophilic aromatic substitution is due to the multiple phenol groups. The hydroxyl is a powerful electron donor (*+M*) especially under basic conditions (pH: 9-12) where the phenoxide ion is formed, which pushes electrons onto the A- and B-ring, thereby enhancing the nucleophilic potential in specific C_{15} reactive sites.

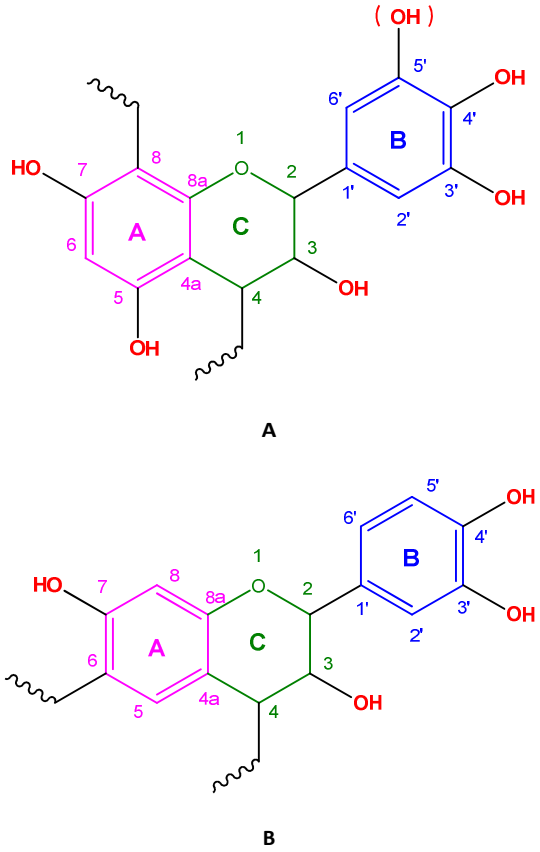


Fig 1. Chemical structure of the C_{15} unit in condensed tannins. C→C linkage between C_{15} units: C4→C8 (A), and/or C4→C6(B).

Under acid conditions the reactivity of the rings towards electrophilic compounds (*e.g.* aldehydes) increases. Phenol groups are *ortho* and *para* directing. Hence, the *meta* phenol groups, which are common on the A-ring, both activate the C-6 and C-8 positions. In contrast, the vicinal di-phenol groups (catechol- or pyrogallol- type B-ring) cause a general activation on the B-ring rather than a specific activation of their corresponding C-ring atoms. Therefore, the B-ring is relatively unreactive during electrophilic substitutions in comparison to the A-ring. It´s reactivity can be enhanced by selecting specific pH and catalyst type. However, from a practical point of view this is not efficient as the reactivity of the A-ring is increased, as well, which increases the polymerization kinetics dramatically.

Further studies on the reactivity of CTs based on model compounds (resorcinol, phloroglucinol, and flavonoids) have been undertaken by selective reactions.[15] These studies showed that a derivatization of the C-8 site or a linkage to

another C_{15} unit at this position is ubiquitous for a derivatization or an advancing polymerization at the C-6 position. These model studies allowed an understanding of the general order of reactivity of the CT-monomer unit carbon atoms (8>6>>3´>4´>5´). However, the molar mass (*Mw*) and the steric hindrances conditioned by the conformation of CTs are factors that must be considered to explain the varied and sometimes unpredictable reactivity.[17]

Under acidic conditions two competing reactions occur: (*1*) the polymeric or oligomeric chain can be degraded to their C_{15} monomers; (*2*) the flavonoid units can condense. The first reaction is thought to be induced by the hydrolysis of the heterocyclic C-ring and its electrophilic attack upon a nucleophilic center of the A-ring.[15]

Under alkaline conditions, epimerization and rearrangements occur. Epimerization of catechin to epicatechin occurs in hot water or diluted alkaline solutions. This epimerization involves only a change in stereochemistry at the C-2 of the C-ring. Under strong basic conditions this epimerization reaches equilibrium in several hours.[15-18] Rearrangement and loss of aromaticity of the C_{15} unit in alkaline medium is also reported.[19]

1.3. Physicochemical properties of CTs

There are few studies on the physical properties of CTs. In general, CTs are low-density amorphous non-crystalline pale yellow-slightly brown solid oligomer/polymers. Numerous tannins are optically active, while their stereochemistry is highly influenced by the C_{15} sequence. Dried tannin extracts are hygroscopic and exhibit a strong absorption in the UV-Vis region with several local maxima (λ_{max}: 250 and 290 nm). At room temperature, CT-extracts are mainly soluble in water, short-chain alcohols (methanol, ethanol), and acetone aqueous solutions, and yield an acid environment with a sharp “puckering” and “astringent” flavor.

They yield colloids in water were they form viscous solutions (*e.g.* 40-45 wt.%, 5 mPa/s at 20 °C) due to the strong hydrogen bridge formed between the -OH groups and the water molecules.[7,20] The viscosity depends on the CT concentration, the dispersity, the topology and the relation of hydrophilic/hydrophobic domains. The viscosity of some tannin extracts is increasing the difficulty to formulate CT-based materials or to spray CT based resins, especially in the wood-based composite industry.[7,10]

In addition, CTs are thermo- and UV- labile compounds prone to oxidation. The residual weight at 600 °C oscillates between 40-50 % as a consequence of decomposition processes between 150-300 °C.[22] However, the thermal behavior is strongly associated to the *Mw* and the chemical structure.[23,24] In general, CTs decompose in three main degradation steps according to their specific chemical structure and their linkages. The B-ring stripping process at temperatures between 200-250 °C opens up the C_{15} structure, which enables sequential degradations.[26]

Considering that CTs are bio-polymers, the glass transition temperature (T_g) is an important variable to be considered for CT-application in materials engineering. Their T_g is strongly associated to the *Mw*, the purity grade, and the moisture content. The T_g of native tannin oscillats between 120 and 180 °C. In general, it is difficult to detect the T_g in CT samples. In addition, the reproducibility for the values is very low, regardless of the experimental parameter variation using DSC (Differential Scanning Calorimetry). [37]

2. Chemical modification of CTs

2.1. Main derivatization pathways

Derivatization is the process of chemically modifying a compound to produce a new structure. The new properties of these structures can be suitable for selected purposes. Thus, by selectively changing the properties through chemical modification, the range of potential utilization of the original compound can be increased.[8,15] In case of CTs, modification of the native tannin extracts can overcome drawbacks like low solubility, high viscosity, and too high or too low reactivity. Modification allows a further enhancement of these properties under consideration of the requirements for the selected application. According to the recent literature, derivatization seems to be an appropriated way to use this renewable product as a building-block for bio-polymer engineering and chemical synthesis.[15,25-27]

Several CTs have been subjected to a large variety of derivatization reactions. This section has been restricted to the identification and the discussion of the most relevant work according to the impact on physicochemical properties.

Table 2 and 3 show the main modification reactions reported in polyphenols and the common derivatizing agents used during modification, respectively. According to the reactivity of the CT monomers discussed above, functionalization on the -OH groups, as well as the nucleophilic positions on the rings, are the most important sites for derivatization (see Fig. 1).

The degree of chemical modification (DS) depends on the polyphenol type, the derivatizing agent, and the experimental conditions. A wide range of strategies to get tailored derivatives as additives[28], fiber reinforcements[29], biological active compounds[30], thermosetting systems[31], foams[32], and copolymers[33] are documented based on either one-step synthesis, or multiple-stage reactions.

In CT monomers there are three sites for derivatization. There are reactions that are selective towards one of these three derivatization sites.[34] The A-ring can be derivatized at the C-5 or C-7

-OH group or at the C-6 position (see Fig. 1). On the B-ring, derivatization takes place mainly at the C-3′ or C-4′ -OH group (or additionally at the C-5′ -OH group in case of delphinidins or gallo-pyrogallols. The C-ring can be modified at the C-3 -OH and at the C-4 inter-C_{15} linkage. In C_{15} terminal units of CTs, derivatization may occur at the C-8 position.[35]

O-acylation. Among all of the reactions involving -OH groups of polyphenols, esterification is probably the easiest to carry out considering the reaction parameters and the reactants used.[36] The O-acylation (esterification and *trans*-esterification) can introduce a wide range of functionalities by several different methods (Table 2), and derivatizing agents (Table 3). Reactions with acid chlorides and anhydrides are typical for CT modification. Several thesis, papers, and patents outline methods for the preparation of functional derivatives.[15,36]

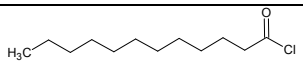
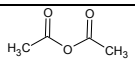
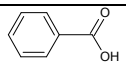
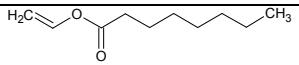
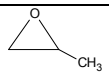
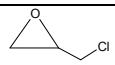
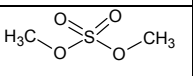
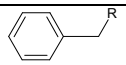
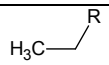
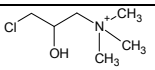
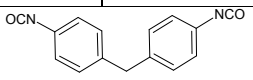
The synthesis of CT-ester derivatives can be achieved by several methods such as Fischer esterification, alcoholysis of acid halides or anhydrides[15], novel approaches with catalyzers[51,52], microwave irradiation[53], and replacing halides by less toxic organic moieties are also reported.[54] Fischer esterification is the classic route to prepare CT-esters. In the course of this reaction an acid reacts with –OH groups via nucleophilic acyl substitution. Aliphatic alcohols are relatively reactive in Fischer esterification, while in the case of hydroxylated phenols the reaction has to be enhanced by a dehydrating agent or by other strategies.

Table 2. Main modification reactions in CTs and chemical-related polyphenols.

Reaction-type	Derivatizing agent	Ref.
Functionalization of the –OH group(s)		
Esterification	Acid chlorides, anhydrides, or carboxylic acids	15
Alkylation	Acid chlorides or alkylene oxides	32,33
Urethanization	Isocyanates	38,39
Dealkylation	HCl	37
Oxidation/reduction	Redox agent ($K_2Cr_2O_7$, $KMnO_4$), enzymes	40
Chelate formation	Transitional metals (Fe^{3+}, Cu^{2+}, Zn^{2+})	41
Benzoylation	Benzoic acid/H^+	7
H/deutherium exchange	Deutherated solvents (D_2O, EtOD)	42
Functionalization of the aromatic ring(s)		
Alkylation	Alkyl halides/K_2CO_3 or OH^-	43
Acetylation	CH_3COO^-	25
Methylolation/ condensation	Aldehydes/H^+ or OH^-	44
Halogenation	Halogens (Cl_2, Br_2, I_2)	45
Sulphonation or sulphitation	H_2SO_4 or Na_2SO_3	30
Carboxymethylation	Ethyl chloroacetate	46
Amination	NH_3/H_2O	47
Nitration	HNO_3/H_2O or HNO_3/AcOH	48
Nitrosation	$NaNO_2/H^+$	49
Phenolation	Phenol	50
Depolymerization	Mercaptan/H^+	34

For instance, acid halides offer a higher reactivity in comparison to their corresponding carboxylic acids or anhydrides. Therefore, CTs can be easily acylated this way.[55]

Table 3. Common derivatizing agents used for chemical modification of CTs and chemical-related polyphenols.

Reaction type	Chemical	Structure	
Esterification	Lauroyl chloride		
	Acetic anhydride		
	Benzoic acid		
Trans-esterification	Vinyl octanoate		
Alkoxidation	Alkylene oxides	 1. Propylene oxide	 2. Epichlorohydrin
Alkylation	Organic esters	 1. Ethyl carbonate	 2. Dimethyl sulfate
	Benzyl halides (R: Cl, Br, I),	 1. Mercaptan (R: SH)	 2 Ethyl halides (R: Cl, Br, I)
	Functional halures	 1. TCA	 2. TCP-TMA
Urethanization	MDI		

TCA: tri-chloro acetic acid, TCP-TMA: N-(3-chloro-2-hydroxypropyl) trimethyl ammonium chloride, MDI: methyl di-isocyanate.

The reaction is often carried out in the presence of hydroxides or organic (pyridine, ionic liquids, amines) bases. The base-catalysis assists the activation of the -OH for an electrophilic

attack (alcoholysis) of anhydrides in a comparable way as acid halides. Anhydrides are less reactive than acid halides, but the first one is often used for modification in order to gain structural information of products and intermediates. [25,56] In comparison to low *Mw* polyphenols, CT derivatives are often synthetized under less drastic conditions according to temperature and reaction time and this is independent of the derivatizing agent.[57,158]

This is caused by the fact that alcoholysis reactions are often affected by steric hindrances. Bulky groups slow down the reaction, resulting in a defined -OH reactivity order, where the A- and B-ring aromatic -OH groups show a higher reactivity than the C-ring aliphatic -OH groups.[15]

However, beyond the noticeable differences between –OH reactivities, the conformational structure of CTs influences reactivity even at high temperatures and pressures. Tannin from mimosa and Quebracho tannin are considered less-reactive CTs upon certain modification reactions (oxybutylation and oxypropylation) than the pine tannin. [82,83] The C4→C6 linkages confer a peculiar branched configuration, which maximizes the steric hindrance upon alkylation. Such results contrasts to the high reactivity of pine tannins (PRBT and PPBT), described as *quasi*-linear conformational oligomer-chain. Anyway, it has to be taken into account that apart from steric hindrances, all the mentioned tannins exhibit very similar *p*Ka values of their OH-groups.

Table 4. Acylation (esterification and *trans*-esterification) reaction in CT-monomer unit, and CTs.

CT	DA	T (°C)	t (h)	Solv.	Cat.	Yield (%)	Ref.
PRBT, QT	VA	20 and 70	48	H_2O, THF, DMSO	KOH ,TEA	n.i.	16
PRBT	AH	65	16	-	MEI	n.i.	29
		65	4 and 6	-	MEI	n.i.	
		70	4	2-Pen/ Acet.	MEI	0-134	59
PRBT, QT	Hld.	75	24	Chlor.	Py	8-24	15
Nutgall tannin		22	2	Acet./ Py	TEA	n.i	66
Wattle tannin		20	n.i.	1,4 DOX	Py	n.i	67

CT: condensed tannin, DA: derivatizing agent, T: temperature, t: time, Solv: solvent, Cat: catalyst, PRBT: radiata pine bark tannin, QT: quebracho tannin, MEI: methyl imidazole, n.i.: no informed, VA: vinyl acetate, AH: anhydrides, Hld.: halides, THF: tetrahydrofuran, DMSO: dimethyl sulfoxide, Pen: pentanone, Acet: acetone, Chlor.: chloroform; Py: pyridine, DOX: dioxan.

On the other hand, specific CTs reactivity is conditioned by the reaction type. For instance, hydroxypropylation reaction takes place on the A-ring at low derivatizing agent content, while isocyanates reacts preferably on the B-ring. So, the selectivity seems not to be related exclusively to the acidity values of -OH groups.[15,27]

Direct acylation of CTs with short-chain chemicals is strongly dependent on the experimental conditions. Pyridine and aliphatic amines are frequently used as catalyst, and chloroform, acetone, or aqueous solutions are the best choices as solvents, considering the low solubility of native CTs in organic liquids. O-acylation of CTs with alkyl halide and long-chain esters in chloroform and polar solvents, respectively, provided low yields regardless the stoichiometry of the derivatizing agent. Therefore, a high *Mw* of CTs requires a higher reactivity of the reaction agents in order to favors high yields.[49]

Table 5. O-acylation (esterification and *trans*-esterification) of CTs*.

CT	DA (equiv.)	T (°C)	t (h)	Solv.	Cat.	Yield (%)
Reaction with lauroylCl (esterification)						
PRBT	3	75	24	Chlor.	Py	10
	Excess					24
QT	3					19
	Excess			-		8
Reaction with vinyl laureate (*trans*-esterification)						
PRBT	Excess	20	48	THF	KOH	7
QT						12
PRBT	Excess	70		DMSO	TEA	21
QT						8

CT: condensed tannin, PRBT: radiata pine bark tannin, QT: quebracho tannin, DA: derivatizing agent, T: temperature, t: time, Solv: solvent, Cat: catalyst, Chlor.: chloroform, THF: tetrahydrofuran, DMSO: dimethylsulfoxide, TEA: trimethylamine, *according to Hadley[15].

While ionic liquids have been used for the derivatization of flavonoids and other chemical-related polyphenols[15,29,59] the utilization of catalysts with polar functionalities such as carbodiimides, triazoles, and organic salts (chloroformates) has not been used in CT derivatizations. The Table 4 shows a wide range of experimental conditions used for modification via O-acylation. [60-67]

Alkylation (etherification). CTs were etherified by several methods including the Williamson ether synthesis and alcoholysis of epoxides.[68] The Williamson ether synthesis, where a tannin-alkoxide reacts with an alkyl halide based on the differences in nucleophilicity[69], is the more feasible method to prepare CT-ether derivatives. Considering the acidity of –OH in CTs, organic or inorganic catalyzers can be utilized to increase the yield of this reaction (*e.g.* NaOH and

K_2CO_3).[15] A major drawback of C-alkylation is the possible side reaction for natural phenols and CTs. This reaction can be minimized by using polar aprotic solvents (DMSO, THF, pyridine, 1,4-dioxane, acetone) instead of short-chain alcohols (MeOH, EtOH) and water. Polar aprotic solvents are able to increase the bonding strength between the proton and the oxygen of the phenolic hydroxyl group, which decreases the nucleophilicity of this group. In consequence, the carbon atoms *ortho* and *para* to the phenoxide compete in the nucleophilic displacement.[69]

Alkyl bromides are more reactive than alkyl chlorides in CT-etherification reactions, which leads to higher yields. As the reaction is induced by a S_N2 mechanism, the primary alkyl halides are ideal for supporting E2 elimination on secondary substrates.[15]

Asymetric ethers should be synthesized by reactions between sterically hindered alkoxides and the less sterically hindered halides.[43,70] Other strategies comprises alkylation with carbonates using phosphines[71], and nitrogenous buffers[72] instead of alkali hydroxides and amines[73] led to reasonable yields. However, mentioned strategies have not been used for high *Mw* polyphenol modifications.

On the other hand, studies on the selective/non-selective alkylation of CTs described the use of ethylene oxide, alkyl sulphates, and halides as derivatizing agents.[15] Other commercial CTs have been alkylated using agents like oxides, organic sulphates, acid chlorides, and halides. These alkylation strategies lead to mono-alkylation of the C_{15} unit as the major reaction product.

Double-functionalization using mixtures of mercaptans and electrophilic agents have been used to increase the biological activity of the derivatives.[75] This strategy yields a highly homogeneous product, because of the multiple reactive sites in polyphenols where bulky-halides induce the O-acylation instead of the alkylation.[43] Therefore, short-chain derivatizing agents are preferable in comparison to bulky derivatizing agents.

Experimental conditions for the alkylation of CTs are listed in Table 6.

Table 6. Experimental condition for CTs alkylation.

CT	DA	T (°C)	t (h)	Solv.	Cat.	Ref.
PRBT	DGD and PGDE	80-90	GT	H_2O	NaOH	74
Tannin*	1-BO	60	2	DMF	K_2CO_3	66
Tannin*	TCP-TMA C/F	48	1.5	H_2O	NaOH	75
MBT	TCAA, Resorc., Catech.,Na$_2$SO$_3$	86 and 90	2, 1.5, and 1.7	H_2O, OA, H_2O	n.u.	30

CT: condensed tannin, PRBT: radiata pine bark tannin, MBT: mimosa bark tannin, *: unspecified, DA: derivatizing agent, T: temperature, t: time, Solv: solvent, Cat: catalyst, DGD: diglycidyl di-epoxide, PGDE: polyglycidyl di-epoxide, TCP-TMA: N-(3-chloro-2-hydroxypropyl) trimethyl ammonium chloride, BO: 1-bromo octane, TCAA: trichloroacetic acid, C/F: condensation/formaldehyde, Resorc.: resorcinol, Catech.: catechol, GT: at gelation time, OA: 1-octyl alcohol.

Epoxides are used for the alkylation of CTs in a wide range of temperature (20-200°C). High pressure and the combination of less polar aprotic solvents (toluene and acetone) or aqueous solutions are used to enhance the derivatization reaction with alkylene oxides.[15,37,38,76,77] The chemical structure of CTs, the *Mw* distribution, and the –OH pattern significantly affect the degree of substitution (DS).[25-27,37,38]

2.2. Alkylation of CTs with alkylene oxides

Alcoholysis of epoxides is a simple method to prepare hydroxyalkyl ethers. CT-ethers are used as chain-extenders in polyurethanes or as a co-monomer for polyester co-polymerization.[77,78] The ring opening reaction of an epoxide is an efficient route to prepare ethers from high *Mw* polyphenols.[79] On the other hand, alkylene oxides can be used for the preparation of simple phenol- and flavonoid-derivatives.[15]

The "oxypropylation" reaction and related short-chain oxoalkylation is an alternative pathway for the functionalization of CTs and lignin. This reaction has been extensively studied also for the modification of non-phenolic biopolymers and is one of the most attractive etherification alternatives considering the dramatic impact in properties.[80,81]

The general reaction mechanism of short-chain alkylene oxides, like propylene-, ethylene-, and butylene oxides, is determined by the high strain within the epoxide rings. This leads to their high reactivity compared to larger cyclic ethers. Epoxide ring scission can occur under neutral, basic, or acidic conditions, at any of the ring carbons. This high reactivity and flexibility in ring scission are the two major reasons for the feasibility of these short chain alkylene oxides for high *Mw* polyphenol modification.

Under basic or neutral conditions monoalkyl-substituted epoxides react predominantly at the less substituted carbon, due to steric effects (S_N2 type mechanism). Under acidic conditions the phenate attack at the more substituted propylene oxide-carbon increases, but the attack at the less substituted carbon is still predominant. [15,81]

Acid-catalyzed ring opening occurs with a partial carbenium ion character on the reaction center. This is more in agreement with a S_N1 type mechanism. The rate constant of

alkoxylation (k) highly depends on the *p*Ka of the -OH group.[15] The order of reactivity is the following: $k_{phenolic\ (A\text{- and B ring})}$ -OH>$k_{primary}$ -OH> $k_{secondary\ (C\text{-ring})}$ -OH> $k_{tertiary}$ -OH. However, CT-modification via acid-catalysis have not been reported yet.

Base-catalysed ring opening reaction is the most common pathway in order to modified CT with alkylene oxides. Typical catalysts are KOH or NaOH. Polyphosphazenium, aluminum tetraphenyl porphine, caesium hydroxide, and tertiary amines show an excellent results for simple phenol and flavonoid modification, as well,[50] while mineral bases still being the most useful catalysts.

Table 7. Oxypropylation of CTs with alkylene oxides.

Polyphenol	PO (equiv.)	Yield (%)	Conditions
QT[15]	1	93	T: 110 °C t: 24 h Catalyst: TEA Solvent: toluene, alcohols DA : propylene oxide (PO) Parr reactor
	3	93	
	5	79	
	10	47 (CE)	
	20	28 (CE)	
PRBT[15]	1	99	
	3	100	
	5	96	
	10	84 (CE)	
	20	58 (CE)	
PPBT[81]	1	91	T: 22 °C t: 24 h Catalyst: NaOH Solvent: water DA: PO p: 1 atm
	2	86	
	3	89	
	4	92	
	5	94	
	6	85	
Gambier CT[82,83], MBT[83], QT[83], PPBT[83]	40/60*	n.i. (CE)	T: ≥150 °C t: 1-24 h Catalyst: KOH Solvent: water DA: PO[82], BO[83] Parr reactor
	30/70*		
	20/80*		
	10/90*		

CT: condensed tannin, PRBT: radiata pine bark tannin, PPBT: pinaster pine bark tannin QT: quebracho tannin, DA: derivatizing agent, PO: propylene oxide, BO: butylene oxide, MBT: mimosa bark tannin, *(CT/alkylene oxide ratio, w/w), CE: chain extended derivatives, THF: tetrahydrofuran, DMSO: dimethylsulfoxide, TEA: trimethylamine, n.i.: not informed.

The oxyalkylation of CTs has been used recently.[15,81-83] Modification was achieved mainly under drastic experimental conditions (pressure and temperature)[82], as well as at room temperature.[81] The most comprehensive research concerning CT derivatization with PO and butylene oxide using a Parr reactor was conducted by Hadley[15] and Arbenz and Avérous[82-83], respectively (Table 7). A positive linear relation between the PO molarity and the yield of oxypropylated CTs with an optimum ratio at 1:3 (OH:PO) was reported.

In addition, a strong relationship between the DS, and selected physico-chemical properties was established when CT-monomer units (catechin) were used.

Alternative strategies based on less drastic conditions (22 °C, 1 atm) have been recently described in the literature.[25-27] *P. pinaster* tannin oxypropylation improves the solubility of derivatives in several organic solvents, as well as the thermal resistance. Under the mentioned conditions the derivatives show non-oligomerization of the chain,[81] while pressure conditions yield chain extended CT-derivatives.[82,83]

More complex epoxides such as di-epoxides of diglycidyl ether and polyglycidyl ether type have been used to cross-link bark tannins. The variation of the pH showed that the opening of the epoxide moiety was favored in basic media.[74]

The oxypropylation reaction is a common strategy to modify the physicochemical properties of natural polyol sources and this is particularly noticeable in the case of PPBT.[81] The effect of internal plasticization of PO-modified CTs was extensively studied.[32-36] The functionalization or chain-grafting degree improves the thermal properties and solubility.[77,81]

The solubility in non-polar solvents increases due to the derivatization and this extends the utilization potential of CT in material science, mainly for thermoplastic engineering. The type of alkylene influences the solubility of the derivatives, *e.g.* propoxylation leads to a better solubility than butoxylation.[15,82]

Some systematic assays have been performed regarding the effect of chemical modification on CT-solubility trends. Hydroxypropylation of high purified *P. pinaster* bark tannin improved the solubility in short-chain alcohols, as well as THF, dioxane, and acetic acid, while in consequence the solubility in polar solvents (H_2O, acetone, acetonitrile) was reduced. The solubility trend of modified CTs follows a non-lineal behaviour for protic and a linear trend for protic solvents at the entire range of experimental modification degree (DS: 0.1-4.7). The trend suggests a cross-over point associated to specific interaction of the solvents proton with specific groups (–OH, grafting) in function of the aromatic ring-type, and conformation.

However the influence of the extraction method of the neat CT on CT-derivative solubility behavior have not been well-clarified. Hydroxypropyl derivatives from PRBT, obtained under pilot-plant condition, exhibited a peculiar behaviour. As expected, the modification changed the derivatives' solubility in several solvents significantly. However, the difference in solubility in function of the DS was negligible. Concomitants such as carbohydrate moieties, and terpenes traces in the extract might affect the solubility trends in a high extent.

On the other hand, the *Tg* of CTs decreases due to oxyalkylation. The *Tg* value reduction is determined by two factors: (*i*) the

intramolecular hydrogen bonding rupture and (*ii*) the increasing free volume.[56] Because of the advantage in solubility, and thermal resistance CT-hydroxyalkyl derivatives were used for polyurethane foams[77], and for resin formulations.[73, 81]

Hadley[15] reported a significant decrease of the *Tg* value (Δ*Tg*: ~70°C) when catechin was oxypropylated. This decrease followed a linear trend with increasing DS (1→5). However, it was difficult to establish a correlation between DS and *Tg* values when PRBT and QT were used.

In addition, PPBT modification decreased the *Tg* in 0.9 °C/wt. % upon oxypropylation, while PRBT derivatives showed a reduction of 0.7-0.8 °C/wt. %. The *Tg* rate reduction in both cases was similar to the plasticization rate reported for oxypropyl-lignin (1.0 °C/wt. %). The aromatic content, the rigidity, as well as the *Mw* of the oligomers seemed to be the main factor that affect the *Tg* reduction in modified CTs.

2.3. Other derivatization reactions

Besides acylation and alkylation as traditional strategies to modify CTs, several other derivatization methods were used. Nucleophilic depolymerization[84], chelation formation[85], sulphitation[86] and the Mannich reaction[87] are four routes for CT functionalization that are described here (Table 8).

Nucleophilic depolymerization. Is a well-known derivatization reaction utilized for structural characterization of CTs. There are two derivatization reaction types: thiolysis and phloroglucinolysis. The former one utilizes benzylmercaptans (thiol, R-SH) and the second one utilizes phloroglucinol as derivatizing agent. In both cases the C_{15}→C_{15} interflavanol linkage is cleaved and, thereby, the polymer chain is fractionated. These reactions yield C-4 thioether or C-4 phloroglucinolate derivatives, respectively.[34] The low *Mw* derivatives are analyzed by chromatography in order to gain insights regarding the chain-length and the C_{15}-unit composition.[88] The thermal stability of these derivatives dramatically changes after the chemical modification. However, such reactions have not explored as strategy for developing novel based-derivatives materials.

The chelate formation. Is a complexation reaction between transitional metal (*d* electron acceptors) and vicinal -OH groups, which is typical for catechol based B-rings, 4,5-OR based C_{15} units, or flavonol-3,4-*ol*-based CTs. The chelation of CTs with cations can lead to a strong alteration of the biological properties of the modified CTs.[41,105] The chelation reaction is often irreversible and can yield solid derivatives with enhanced biological properties.[89] Beyond the bio-active propertiy characterization of CT-complexes, factors affecting chelation stability such as (1) charge on the metal ion, (2) nature of the A- and B-ring as ligands, (3) stoichiometry of chelation, and (4) supramolecular structure have not been systematically studied.

Sulphitation. Is a common reaction that alters the solubility of CTs during the extraction process. [7] This reaction was applied in the Quebracho industry to improve the solubility of high *Mw* oligomers and hence to complete solubilization from the hardwood.[9] This reaction affects the particle size of the tannin and enhances the selective solubility according to the lability of specific linkages in the A and B-ring. Sulphitation, which is generally accomplished by adding sodium sulphite into aqueous sodium hydroxide or sodium carbonate for CT extraction can change the solubility and viscosity of tannin.[81,86] The effects of sulphitation on viscosity, acidity, and reactivity of CTs depend on the bark species.[10] However, CT-sulphite derivatives that exhibit enhanced solubility in high polar solvents have not been used as block polymer for biomaterial design.

Table 8. Others derivatization reactions for CTs

CT	DA	T (°C)	t (h)	Solv.	Cat.	Yield (%)	Ref.
PAs	BMC	90	2*	MeOH	HCl	88	90
	BMC and PG	80 and 20	50 and 48	EtOH and DOX/ H_2O	AcOH and HCl	25-38	91
MBT	$CuCl_2$/ NH_3	20	n.i.	H_2O	n.u.	n.i	92
PRBT	F	80	0.3		HNO_3		93

CT: condensed tannin, DA: derivatizing agent, T: temperature, t: time, Solv: solvent, Cat: catalyst,*min, PAs: procyanidins, PRBT: radiata pine bark tannin, MBT: mimosa bark tannin, BMC: benzylmepcantan, PG: phloroglucinolysis, F: formaldehyde, n.i.: no informed. n.u.: no utilized.

The Mannich reaction. Is an alternative route for CT functionalization. In many cases such derivatization is combined with a condensation reaction between CTs and formaldehyde. Carboxylic acids, cationic salts, and keto-acids functional groups are often graft-functionalities. This reaction comprises a nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base[87]. CTs are modified into derivatives with a wide range of applicability in the chemical and cosmetic industry.[89] However, research has been focused on CT-derived materials characterization instead the understanding of key points, such as mechanism involved when CT is used as block co-polymer.

Despite that there are lack of systematic studies providing valuable insight of the influence of chemical modification in a wide range of experimental conditions, the Fig. 2 illustrates the most common applications of modified CTs in function of the chemical structure of the grafted-chain.

The physicochemical properties of CT-derivatives are correlated to the DS, the type of the derivatized polyphenol, the derivatizing

agent, and the specific sites where the derivatization occurs. In general, the derivatives exhibit considerable changes in the physicochemical properties in comparison to the corresponding native polyphenols.[21,77]

Solubility and viscoelastic properties. Acetylation and alkylation of CTs can alter the solubility[81], reactivity[81], the *Mw* distribution[56], and the thermal, and rheological properties[15] to a high extent. Hydrophobic modifications improve the interactions of CT with less polar solvents, bio-polymers[28,29,59], and membranes[94], and reduce the water binding capacity of processed bio-polymers[25-26]. In the context of CT-based polyurethane resin synthesis[33], partially benzoylated CTs alter the solubility of the highly polar tannins in order to match the solubility of the diisocyanates and thus to allow the polymerization reaction.[38]

Reactivity. CT reactivity was severely affected by modification. The influence of the grafting on the electronic configuration of aromatic rings (specifically the nucleophilic centers) was the reason why the dramatic reduction in reactivity when aromatic –OH were replaced by secondary aliphatic moieties.

Thermal properties and reaction kinetics. A higher DS usually leads to an increased thermal stability and is associated with a higher degradation onset temperature.[16] Long-chain grafting on *P. radiata* bark tannin and Quebracho tannin retarded the decomposition.[16] In detail, both the substitution pattern on the B-ring and the C_{15}→C_{15} linkage type affects the stability and the degradation onset. By benzoylating tannins that were used in polyurethane chemistry the -OH/C_{15} relation was reduced, which decreased the kinetics of the reaction with the isocyanates and led, in consequence, to a better network formation and enhanced thermal stability. While mechanisms that dominate the thermal decomposition of certain derivatives are known, the thermo-protective role of derivatives used as block co-polymer in materials such as polyurethane foams and selected thermoplastics is unclear.

Biological properties. The effects of chemical modifications on the biological properties of flavonoid derivatives has been studied by antioxidant and anticancerogenic screening.[17] Derivatization pattern in specific sites improved the therapeutic activity[50] and the derivatives' feasibility for wood preservation against termites and fungi.[81] CT derivatization by sulphonation, catecholation, and phloroglucinolation enhanced the bacteriostatic power and the biodegradability of CT-based rigid foams.[30]

3. Utilization of CTs with an emphasis on material science

The most representative patents according to the impact of the content on databases (United States Patent and Trademark Office and the European Patent Office) and additional bibliographic sources were surveyed. This overview shows several patents (granted or pending) concerning applications of CT. Fig 3. show the evolution of published patents related to CT- and MCT-applications.

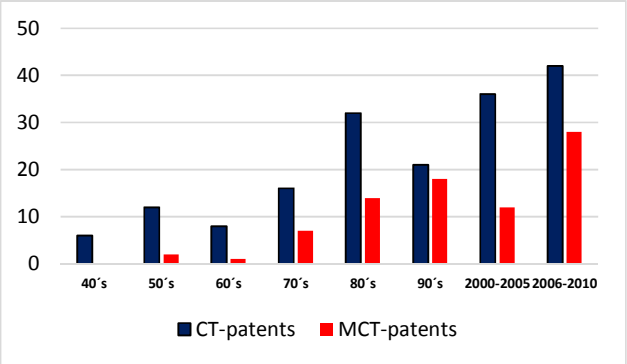


Fig. 3. Evolution of published patents related to CT- and MCT-applications. Patents were surveyed based on the United States Patent and Trademark Office and the European Patent Office databases. CT: condensed tannin, MCT: modified condensed tannin

Table 9. Most cited patents on CT/CT-derivatives applications (1944-1999).

Patent (year)	Assignee	CTs-type/key word
US2354672 (1944)	Resinous Prod & Chem. Co.	CT/resin
US2590760 (1952)	Da Veiga Vinicio	
US3254038 (1966)	Borden Co.	CT/adhesive
US3515556 (1970)	Eastman Kodak Co.	CT/photography film
US3856845 (1974)	Itt	MCT/bark etherification
US3886066 (1975)	Du Pont	CT/non-porous material
US4090919 (1978)	Tanabe Seiyaku Co., Ltd.	CT/protein immobilization
US4558080 (1985)	Dearborn Chemical Co.	CT/polymer
US4595736 (1986)	Betzdearborn Inc.	MCT/aqueous systems
US4944812 (1988)	Henkel Corporation	MCT/corrosion resistance
US5134215 (1992)	Nalco Chemical Co.	MCT/modified cement
US5158711 (1992)	Mitsubishi Nuclear Fuel Co.	MCT/adsorption
US5270083 (1993)	Cecco Trading, Inc.	MCT/preservative
US5659002 (1997)	Nalco Chemical Co.	MCT/Mannich polymers
US5698601 (1997)	Bayer Aktiengesellschaft	CT/PU foams
US5830315 (1998)	Betzdearborn Inc.	MCT/water purification
US5912037	W. R. Grace & Co. -	MCT/beverages

(1999)	Conn.	
US5977287 (1999)	Betzdearborn Inc.	MCT/aqueous systems

CT: condensed tannin, MCT: modified condensed tannin, PU: polyurethane.

Before the 80´s, CTs and CT-derivatives were used for several commercial applications like traditional leather tanning, adhesive additives, vinification, for pharmaceutical purposes, asphalt additives, dispersants, and in medicine, as well as additives for tiles, floorings, and drilling muds.[15] However, the most cited patents between 1940 and 1980 describe the use of native tannin for conventional applications.

Table 10. Recent most cited patents on CT/CT-derivatives applications.

Patent (year)	Assignee	CTs-type/key word
US6478986 (2002)	Tanac S.A.	MCT/coagulant
WO2004058843 (2004)	Borden Chemical Australia Pty	CT/binding agent
EP1437419A1 (2004)	Tanac S.A.	CT/bioactive
US20060084718 (2006)	Stancliffe Mark R.	CT/Binder
WO2008079652A1 (2008)	Gen Electric Co.	CT/polymeric coagulants
US7611632 (2009)		CT/co-polymer
US7998351 (2011)	Vinod Kumar Rai	CT/coagulants
US7998351B2 (2011)		
US20120148740 (2012)	Yang Chia-Wei	CT/epoxy resins
WO2012162684A2 (2013)	E.I. Du Pont De Nemours & Co.	CT/rigid foam
WO2013010668 (2013)	Silvachimica S.R.L., Universite' De Lorraine - Institut Enstib-Lermab	
WO2012162653A3 (2013)	E.I. Du Pont De Nemours & Co.	
US20130252909A1 (2013)	University of Iowa Research Foundation	CT/HIV inhibitors
EP2805 943 A1 (2013)	Albert-Ludwigs-Universität, Freiburg	MCT/propylene oxide
US8642088 (2013)	Wisconsin Alumni Res. Foundation	CT/chitosan-composites
US20140093720 (2014)	E.I. Du Pont de Nemours & Co.	CT/rigid foam
EP 2617792 A4 (2015)	Korea Advanced Inst Sci & Tech, Inno Therapy Inc.	CT/adhesives

CT: condensed tannin, MCT: modified condensed tannin.

As dispersants, CTs can alter the viscosity of various solids. It reduces the viscosity in clays to improve the manufacturing of bricks and pottery.[18] A tannin based concrete additive provides improved plasticity, uniformity, flowability, and reduced shrinkage of the concrete.

The CT capacity to immobilize metals and macromolecules has been used for the design of tannin-based products (Tanfloc® and Silvafloc®) to clean water by flocculation[95-98], and to recreate ecosystems. Collagen-tannin fiber membranes, which are selective to UO_2^{2+} [99], tannin hydrogels[100], and tannin-rigid foams[101] have been utilized to remove harmful chemicals from aqueous solutions, as well. CTs were also immobilized on substrates for the selective complexation with proteins. Such immobilization on inert and/or active matrices was also used to capture chemical compounds for further analysis[102-104], and in general to manufacture absorbent composites[105]. Complexed CTs are used to inhibit fouling on vessel surfaces[106], as polyphenol containing algae extracts are an efficient bio-based strategy to control harmful marine populations[208]. In addition, applications were invented for purification technologies[40,75,92,93], antioxidant films[107], and cosmetics[55]. Although the pharmaceutical use of CTs is well-known and applied, several investigations reported new properties and applications in alternative medicine in the last 60 years. Potential applications include prevention of chronic diseases, antimicrobial uses, antitumor activity[108], and cardio-protective effects[109].

On the other hand, CT-derivatives) were often used after 80´s. Modified CTs play a key role in application areas where properties such as high miscibility and solubility in a non-polar medium, enhanced/suppressed reactivity, biological activity, and high thermal resistance are critical factors to consider. Derivatives instead of native CTs are useful in order to improve physicochemical properties and durability of thermoplastics. Functionalization enables high miscibility in biodegradable polymer blends such as poly(lactic) acid (PLA)[16,18], and improves flexibility in polyurethane-based materials.[81] Despite this specific chemical modification, oxyalkylation and partial acetylation are strategies to slow down the kinetic of complex reactions. There are no reports describing the understanding of the kinetics of the polymerization mechanisms, the polymerization stages, and the rheological behavior of these modified CTs. In addition, CT-modification might diversify properties of CT-based foams. Grafting of CT with aliphatic moieties may affect the ratio of hard/soft segments, which confers a dramatic impact on properties.

4. Concluding remarks and "perspectives" for the future

Considering the wide distribution of condensed tannins in vascular plants, these renewable natural products exhibit greater prospects in materials science beyond its traditional use in the leather industry and as components of adhesive resins.

The applicability of condensed tannins is restricted by high reactivity and poor solubility in organic solvents. A strategy to overcome this limitation is to modify the chemical structure by derivatization reactions. Among many possibilities, acetylation and alkylation, and here especially O-acylation using acid chlorides or anhydrides and alkyl halures, are the most frequent reactions. They change the physicochemical properties of the derivatives for their effective use in the industry and for purification technologies. Condensed tannins modification with conventional chemicals (*e.g.* anhydrides and halides), and propylene oxide affects drastically the physicochemical properties of the derivatives and provide high performance micro building-blocks for material engineering. The utilization of derivatives instead of native tannins has been described in several scientific journal articles and patents. The new trend points out the use of native and modified tannins as components of novel materials essentially based on: (*i*) the condensed tannin´s properties as phenolic biopolymers with high molar mass, and (*ii*) the versatility conferred by the grafting functionalization. In future, is expected that tannin will be used in other research fields beyond medicine, adhesives, and the leather industry. Modified tannin as additive and block co-polymer for thermoplastics (ultraviolet-filter), tannin-based co-polymer with enhanced biological activity, and as macro building-blocks for hybrid resins preparation are a promissing research areas. Acetylation using specific derivatizing agents (non-linear alkyl halide and cyclic anhydrides) might yield useful alternative chemicals in order to tailor properties and diversify applications.

In future, it is expected that tannins, and tannin-derivatives may be play a key-role as nutraceutical products, as well as controlled release promoters, volatile organic compounds (VOCs) sequesters, and moisture retainers in promising research areas such as food science and agriculture.

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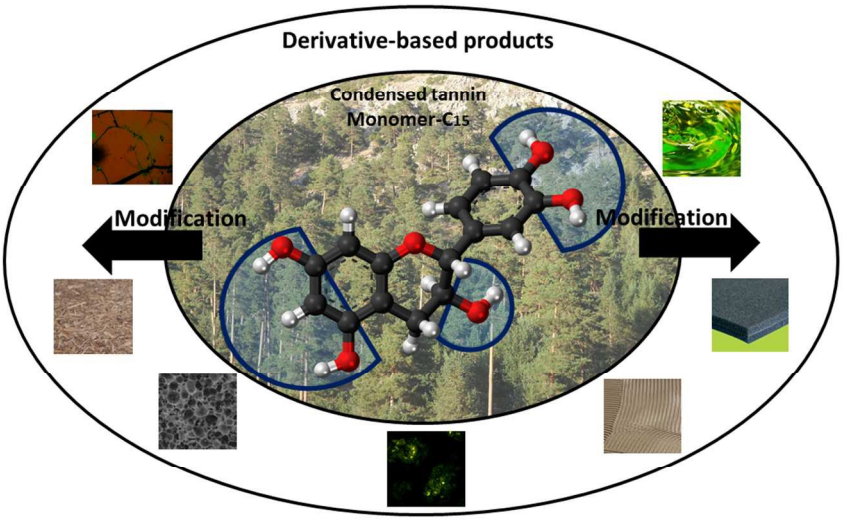

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