Literature Review:

Tripathi, Singh, Bisht, Pandey (2009)

In this paper, the author has given an account of the history, chemistry, biochemistry and biosynthesis of ascorbic acid and application of this small molecule in organic synthesis. The application of ascorbic acid in accessing chiral synthons has also been described. Singh, Bisht, Tripathi (2006)

In this paper developed an efficient and practical method for the synthesis of dienyl tetramic acid derivatives from inexpensive and easily accessible ascorbic acid. The method involves Wittig olefination of the allylic aldehydes obtained from ascorbic acid followed by reaction of the resulting esters with amines to give the intermediate 5-hydroxy lactams. The latter on dehydration with p-toluene sulphonylic acid resulted in dienyl tetramic acid derivatives. The compounds bear structural similarities to the tetramic acid based polyenic antibiotics and the method paves the way for the synthesis of a variety of tetramic acid derivatives with different substituents.

Kang, Oh (2003)

In this paper, a stable derivative of L-ascorbic acid, 2-O-[(3-aminopropyl)phosphinooxy]-L-ascorbic acid (LAAP), was synthesized in moderate yield and its chemical stability and effects on melanin synthesis were investigated. LAscorbic acid was decomposed completely within about 1 hour, while 93% of LAAP remained even after 10 days. Treatment of L-ascorbic acid and LAAP decreased melanin content in normal human melanocytes to 33.8% and 49.1% of control at 2 mM, respectively. Considering chemical instability of L-ascorbic acid, LAAP is a much better whitening agent.

Karwowski, Jackson, Theriault, Barlow, Coen, Hensey, Humphrey (1992)

In this study, the Tirandalydigin is a new tetramic acid antibiotic which was discovered in a screen designed to find compounds with activity against pathogenic anaerobic bacteria. It was named tirandalydigin because it possesses structural features that are common to both tirandamycin and streptolydigin. The producing culture, strain AB 1006A-9, is a Streptomyces and was compared to the streptomycetes that synthesize tirandamycin and streptolydigin. It is closely related to the former culture and was named Streptomyces tirandis subsp. umidus. Tirandalydigin has MICs in the range of 0.5 to 32 micrograms/ml against many pathogenic anaerobes, streptococci, enterococci and legionellae.
**Cramer, Buchweitz, Chem (2006)**
In this paper, a Cylindramide (1) was built up from three components: a hydroxyornithine derivative 7, a tetrazolylsulfone 8, and a substituted pentalene subunit 9. Derivative 7 was prepared in a six-step reaction sequence involving the Wittig reaction and a Sharpless asymmetric dihydroxylation starting from \(N\)-Boc-3-aminopropanal (12). Tetrazolylsulfone 8 was accessible in four steps from dioxinone 22. The synthesis of the pentalene fragment 9 started from cycloocta-1,5-diene 26, that was converted into enantiopure bicyclo[3.3.0]octanidine 29. The latter was functionalized to give derivative 9. The total synthesis was accomplished by inducing \(\text{C} \rightarrow \text{C}\) bond formation by Sonogashira coupling of derivatives 9 and 7 followed by olefination with tetrazolylsulfone 8 under Julia–Kocienski conditions, macrocyclization, and subsequent Lacey–Dieckmann condensation to form the tetramic acid unit. As indicated by extensive \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectroscopic investigations (DQF-COSY, ROESY spectra), the stereochemistry of synthetic cylindramide (1) corresponds with that of the naturally occurring product. ROE data were used for molecular modeling of the lowest-energy structures for cylindramide.

**Courcambeck, Bihel, Michelis, Quéléver, Kraus (2001)**
In this paper, a Novel potential HIV protease inhibitors are obtained by an enantioconvergent synthesis of mimicking Phe-Pro dipeptides, achieved through the coupling between Boc(L)Phe or Boc(L)Tyr and both enantiomers of \(\text{syn}\)-2-benzylpyrroolidin-3-ol and their corresponding pyrroolidin-3-one analogs. The stereochemistry and enantiopurity of intermediate 3-hydroxypyrroolidines 5a and 5b are determined through \(^1\text{H}\) NMR analysis, and through the synthesis and \(^{19}\text{F}\) NMR assignments of the corresponding Mosher’s esters 13a and 13b. The enantiopure compounds 5a and 5b are obtained with 100% diastereoselectivity using specific experimental reductive conditions upon Meldrum’s acid derivatives of activated aromatic amino acids.

**Wang, Yang, Ying, Xiong, Zhang, Cai, Hruby (2002)**
In this paper, A stereoselective method has been developed for the synthesis of 7- and 8-substituted dipeptide beta-turn mimetic azabicyclo[4.3.0]nonane amino acid esters. The allyl groups were introduced in high diastereoselectivity, controlled by 3-phenyl or 4-benzyl groups in pyroglutamic acid derivatives 3 or 9, respectively. The precursors, dehydroamino acids 7 and 13 derived from 5 or 11, underwent asymmetric hydrogenations with Burk's DuPHOS Rh(I)-based
catalysts to furnish alpha-amino acid derivatives in high stereoselectivity. The resulting amino acids 8 and 14 were converted to the beta-turn mimetics 6, 5-bicyclic lactams 1a-d in high yields.

**Fuster, García, Sanz-Cervera, Ramírez, Piera, Simón (2002)**

In this study, a simple, asymmetric synthesis of tetramic acid derivatives is described in this paper. The key step is a carbonyl transfer from carbonyldiimidazole (CDI) to alpha-diimines (I) to form N-alkyl-4-alkylamino-5-methyleneypyrrrol-2-ones (II). In turn, these compounds can be easily transformed into tetramic acid derivatives (III) in two additional steps.

**Hamilakis, Kontonassios, Sandris (2009)**

In this study, the Meldrum's acid has been found to be effectively acylated using the imidazolides of N-protected glycines, X-NHCH₂COOH (X = -COPh, -COMe, -Z, -Boc, -COOMe and -COOEt). The corresponding C-acylation compounds were isolated in high yields and were readily converted to the N-protected tetramic acids. It was shown by pmr spectroscopy that these acids exist as the enol tautomers in DMSO-d₆ solution, whereas in deuteriochloroform solution both the enol and keto tautomers can be observed.

**Gaber, McNab (2001)**

In this paper, the pyrolysis of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) 1derivatives in solution and in the gas-phase takes place by loss of acetone and carbon dioxide to provide ketene intermediates. In particular, methylene Meldrum's acid derivatives 7 often provide methyleneketenes 8, which act as substrates for internal hydrogen transfer leading to cyclisation reactions. The availability of versatile synthetic routes to 7 (in particular R = heteroatom) has led to the efficient preparation of a diverse range of cyclic compounds such as quinolinones, 3-hydroxythiophenes, naphthols, azepin-3(2H)-ones or pyrrolizin-3-ones initiated respectively by 1,3- 1,4- 1,5- 1,6- or 1,7-prototropic shifts.

**Kulkarni, Ganesan (1998)**

In this study, upon treatment with base, N-acylated α-amino acids loaded on Wang resin undergo cyclative Claisen-type condensation to release the tetramic acid in high yield and purity. The use of tetrabutylammonium hydroxide as base simplifies product purification, as it can be scavenged by acidic Amberlyst A-15 ion exchange resin. The diversity of the tetramic acids can be further increased by reductive alkylation of the starting amino acid.

**Singh, Verma, Dwivedi, Tripathi (2006)**
In this paper a Reaction of 5, 6-O-isopropylidene-2,3-bis-O-alkyl ascorbic acid with different amines in the presence of DBU at ambient temperature resulted in the formation of 3,4-bis-O-alkyl-1-alkyl-5-(2-hydroxy ethyl)-5-hydroxy-1,5-dihydropyrrol-2-ones in moderate yields.

**Hwang, Han, Choy (2001)**

In this paper, negatively charged functional organic molecules are intercalatively encapsulated by zinc basic salt (hydrozincite) and layered double hydroxide. Such functional organic-inorganic nanohybrids are realized via coprecipitation reaction involving simultaneous formation of layered inorganic lattice and intercalation of anionic species. The heterostructural nature of these nanohybrids, their particle morphology and textural characterizations are mainly discussed on the basis of Powder X-ray Diffraction and Field Emission Scanning Electron Microscopy results.

**Kim, KIM, Hwang, Baek, Kim, Lee, Chang, Kang (2003)**

In this study, a stable derivative of kojic acid, 5-[(3-aminopropyl)phosphinooxy]-2-(hydroxymethyl)-4H-pyran-4-one (Kojyl-APPA), was synthesized in good yield. The effects of Kojyl-APPA on tyrosinase activity and melanin synthesis were investigated. Kojyl-APPA showed tyrosinase inhibition effect (30%) *in situ*, but not *in vitro*. Kojyl-APPA inhibited tyrosinase activity significantly at 24 h after treatment in normal human melanocytes. It means that Kojyl-APPA is not a direct inhibitor of tyrosinase itself, but it is converted to a potential inhibitor kojic acid enzymatically in cells. In addition, Kojyl-APPA decreased melanin content to 75% of control in melanoma cells and decreased neomelanin synthesis to 43% of control in normal human melanocytes.

**Edwards, Donnelly, Sayre, Rheins, Spielmann, Liebsch (1993)**

In this paper, to find a reliable in vitro alternative test for photoirritancy, the European Commission and the European Cosmetic Association are conducting a 3-year, European validation study. Based on the results of this study, an in vitro photoirritancy method will be selected for incorporation into new international guidelines for photoirritancy testing. As a part of this study, Skin2, a cultured human skin system, was used to evaluate the phototoxic potential of chemicals with known photoirritative properties. The Skin2 ZK1351, a 3-dimensional co-culture system, consists of dermal fibroblasts and a multilayered epidermis comprising
differentiated keratinocytes. This product line has previously been used to evaluate the irritative potential of topically applied ingredients and products. In this study, various concentrations of the test chemicals were applied to the epidermal side of the Skin2 tissue for contact times of 1 h or 24 h and then the tissue was exposed to 2.9 J/cm² of ultraviolet A (UVA) radiation. Treated but nonirradiated tissues were also assayed to predict the cytotoxic potential of the test chemicals, which could mask the phototoxic reaction. After exposure, the tissue substrates were rinsed free of test chemicals and allowed to recover for 24 h.

Aberdam, Roméro, Ortonne (1993)
In this study, the author treated normal human melanocytes in culture with daily UVB radiations. Cumulative increases in UVB doses resulted in proportional increases in tyrosinase activity over the first few days whereas an intermittent pattern of tyrosinase activation was observed after the fifth day of irradiation. This intermittent pattern consisted of latency periods where no melanogenic response was elicited despite exposure to UVB.

Fujiwara, Yamazaki, Siroma (2007)
In this paper, the L-Ascorbic acid (AA) was directly supplied to polymer electrolyte fuel cells (PEFCs) as an alternative fuel. Only dehydroascorbic acid (DHAA) was detected as a product released by the electrochemical oxidation of AA via a two-electron transfer process regardless of the anode catalyst used. The ionomer in the anode may inhibit the mass transfer of AA to the reaction sites by electrostatic repulsion. In addition, polymer resins without an ionic group such as poly(vinylidene fluoride) and poly(vinyl butyral) were also useful for reducing the contact resistance between Nafion membrane and carbon black used as an anode, although an ionomer like Nafion is needed for typical PEFCs. A reaction mechanism at the two-phase boundaries between AA and carbon black was proposed for the anode structure of DAAFCs, since lack of the proton conductivity was compensated by AA. There was too little crossover of AA through a Nafion membrane to cause a serious technical problem. The best performance (maximum power density of 16 mW cm⁻²) was attained with a Vulcan XC72 anode that included 5 wt.% Nafion at room temperature, which was about one-third of that for a DMFC with a PtRu anode.

In this paper, L-Ascorbic acid was applied as a fuel for direct polymer electrolyte fuel cells. The main anodic reaction was the two-electron oxidation of L-ascorbic acid to dehydroascorbic acid, the same as its metabolic conversion. Various precious metals, such as platinum, palladium,
iridium, ruthenium, and rhodium, were available as an anode catalyst for the electro-oxidation of L-ascorbic acid.

**Kokoh, Hahn, Métayer, Lamy (2002)**

In this paper, the electrochemical oxidation of ascorbic acid (AA) at a platinum electrode has been studied in 0.1 M HClO₄. In situ infrared reflectance spectroscopy (SPAIRS and SNIFTIRS techniques) was used to investigate the reaction intermediates. The identification of the different electroreactive species and adsorbed intermediates allowed us to postulate a reaction mechanism for the transformation of AA into dehydroascorbic acid (DHA).

**Rueda, Aldaz, Sanchez-Burgos (2001)**

In this study, the Voltagrams of L-ascorbic acid on a gold electrode show the existence of two oxidation waves but no reduction wave. An analysis of I—E curves was carried out together with the Tafel slopes and reaction orders. The products from the first oxidation were identified by paper chromatography. A scheme is proposed for the overall reaction of the first oxidation together with a reaction mechanism at potentials corresponding to the foot of the wave.

**Ormonde, Neill (2002)**

In this paper, the electrochemical characteristics of ascorbic acid and ferrocyanide were investigated at untreated, surfactant (Triton-X) treated and lipid (phosphatidylethanolamine) treated carbon paste electrodes (CPEs), at carbon powder electrodes, and at CPEs following contact with brain tissue. The results indicate that, following contact with brain tissue, pasting oil is removed (apparently by lipids present in the tissue) from the active surface of the electrode. Resistance and capacitance studies support this interpretation. Electron transfer at the resulting powder-type surface is faster than at the original CPE, leading to a shift in the oxidation wave for ascorbic acid to lower potentials. Adsorption of substrate on the electrode is evident following, but not before, the treatments. Implications for the development of chemically modified CPEs for use in vivo are also discussed.

**Yamazaki, Siroma, Ioroi, (2006)**

In this paper, an electrochemical oxidation of L-ascorbic acid (AA) on carbon electrodes in acidic media was investigated to use AA as a fuel for direct polymer electrolyte fuel cells (PEFCs). A higher current was obtained for the oxidation of AA by modifying glassy carbon electrodes with various carbon blacks. The anodic current density depended on the electrical double-layer capacitance formed by carbon black, Nafion ionomer, and electrolyte solution. Direct-type
PEFCs, in which an aqueous solution of AA was used as a fuel, were fabricated with carbon black as anodes. A maximum power density of 15 mW cm$^{-2}$ was attained at room temperature without any precious metal as an anode catalyst.

**Heller (2004)**

The most unique feature which is their structural simplicity is made possible by the selectivity of their “wired” enzyme catalysts: the cells consist merely of two 7 μm diameter carbon fibers, each coated with a different “wired” enzyme bioelectrocatalyst. On one, catalyzing the two-electron electrooxidation of glucose at a reducing potential, glucose oxidase is co-immobilized in and electrically connected (“wired”) by an electron conducting hydrogel of a reducing redox potential. On the other, catalyzing the four electron electroreduction of O$_2$ to water, bilirubin oxidase is co-immobilized in and electrically “wired” by an electron conducting hydrogel of an oxidizing potential. The cells are the smallest ever built. When the volume of the fibers is 0.0026 mm$^3$, the current of the cell operating at 0.52 V in a physiological buffer solution at 37 °C is 8.3 μA. The 4.3 μW power output of the cell is expected to suffice for the operation of implanted sensors and for the intermittent transmission of the data collected to an external receiver.


Recent developments into technology of proton exchange membrane fuel cells (PEMFC) now allow serious consideration to be given to a direct alcohol fuel cell (DAFC) based on a PEMFC, in which alcohol is used directly as the fuel. This is particularly advantageous for mobile applications, since this will avoid the use of a bulky and expensive reformer. However, the relatively complex reaction mechanism, leading to a low electroreactivity of most alcohols, even methanol, needs the investigation of new platinum-based electrocatalysts, particularly active for breaking the C–C bond when alcohols other than methanol are to be used. Moreover, in order to overcome the deleterious effect of alcohol crossover through the proton exchange membrane, it is necessary to develop new oxygen reduction electrocatalysts insensitive to the presence of alcohols.

**Song, Tsiakaras (2008)**

In the present work, the main aspects related to DEFCs such as electrocatalysts, membrane electrode assembly (MEA) preparation and their corresponding effects on the total cell performance are summarized and discussed. Furthermore, the issues about the disadvantages
such as ethanol crossover and the electrolyte membrane's thermal and mechanical stability, as well as the challenges for DEFC's rapid development and commercialization are addressed.

**Karabinas, Jannakoudakis (2006)**

In this paper, the oxidation of L-ascorbic acid has been studied in sulphuric acid solutions at a bright platinum electrode, by employing cyclic voltammetry, controlled-potential electrolysis and potential-step measurements. On the basis of kinetic parameters—Tafel slopes, reaction orders and pH effects—a possible mechanism is proposed for the overall oxidation process. There is evidence of two rapid and thermodynamically reversible charge-transfer steps which are followed by a slow non-activated desorption and rate-determining step. The kinetics are explained with the aid of the Temkin adsorption isotherm.

**Yangzi, Fujiwara, Yamazaki, Tanimoto, Ping Wu (2008)**

In this paper, direct ascorbic acid fuel cells (DAAFCs) have been studied experimentally; modeling and simulation of these devices have been overlooked. In this work, the author develop a mathematical model to describe a DAAFC and validate it with experimental data. The model is formulated by integrating the mass and charge balances, and model parameters are estimated by best-fitting to experimental data of current-voltage curves. By comparing the transient voltage curves predicted by dynamic simulation and experiments, the model is further validated. Various parameters that affect the power generation are studied by simulation. The cathodic reaction is found to be the most significant determinant of power generation, followed by fuel feed concentration and the mass-transfer coefficient of ascorbic acid. These studies also reveal that the power density steadily increases with respect to the fuel feed concentration.

**Kasmaee, Gobal (2009)**

In this paper, electrochemical oxidation of L-ascorbic acid on polycrystalline silver in alkaline aqueous solutions is studied by cyclic voltammetry (CV), chronoamperometry (CA) and impedance spectroscopy (IS). The anodic electro-oxidation starts at −500 mV versus SCE and shows continued anodic oxidation in the cathodic half cycle in the CV regime signifying slowly oxidizing adsorbates. Diffusion coefficient of ascorbate ion measured under both voltammetric regimes is around $1.4 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$. Impedance spectroscopy measures the capacitances associated with double layer and adsorption around $50 \mu\text{F cm}^{-2}$ and $4 \text{ mF cm}^{-2}$ as well as the adsorption and decomposition resistances (rates).

**Suzuki, Umetani (1997)**
In this paper, an electron transfer reaction between ascorbate in an aqueous solution and oxidizing agents in an organic solution immiscible with water has been studied for the first time by polarography for charge transfer at the interface between two immiscible electrolyte solutions. A reversible electron transfer polarogram at the aqueous|organic solution interface could be observed when tetrachlorobenzoquinone, dibromobenzoquinone and Meldola's Blue were used as oxidizing agents in the organic solution. The oxidation reaction of ascorbate at the aqueous|organic interface was discussed comparing with the reactions at the ordinary electrodes and in homogeneous solutions. The half-wave potentials of electron transfer polarograms at the aqueous|nitrobenzene interface were applied to evaluate the formal redox potential of ascorbate/ascorbate free radical.

**Takagi, Morita (1991)**

In this paper, oxidized and conversion products of L-ascorbic acid (AsA) were studied polarographically. When 2,3-diketo-L-gulonic acid (DKG), the hydrolyzed form of dehydro-L-ascorbic acid (DHA), was dissolved in a deoxygenated neutral buffer solution, two anodic waves were observed to grow with time. One wave had a more negative $E^{1/2} = -0.23$ V at pH 8) than that of AsA. The $E^{1/2}$ of the other anodic wave was coincident with that of AsA. When DKG was replaced with DHA, very similar phenomena were observed. High-pressure liquid chromatography and other techniques revealed that the formation of AsA was due to the reduction of DHA by the 3,4-endiol form of 2,3-diketogulono-δ-lactone, which was formed from DKG and has a stronger reducing capacity than AsA. The possibility of the formation and hydration of the 3,4 endiol form of 2,3-diketogulono-δ-lactone is discussed in relation to its biological significance, together with the stability of AsA and DHA.