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Affinity Chromatography: A Review of Trends and Developments over the Past 50 Years

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Abstract

The field of affinity chromatography, which employs a biologically-related agent as the stationary phase, has seen significant growth since the modern era of this method began in 1968. This review examines the major developments and trends that have occurred in this technique over the past five decades. The basic principles and history of this area are first discussed. This is followed by an overview of the various supports, immobilization strategies, and types of binding agents that have been used in this field. The general types of applications and fields of use that have appeared for affinity chromatography are also considered. A survey of the literature is used to identify major trends in these topics and important areas of use for affinity chromatography in the separation, analysis, or characterization of chemicals and biochemicals.

Keywords

affinity chromatography; affinity supports; affinity ligands; immobilization methods; applications

1. Introduction

Affinity chromatography is a form of liquid chromatography that uses a biologically-related binding agent as the stationary phase [1–5]. This technique has been used for decades for the isolation and purification of specific targets by taking advantage of the selective and reversible binding which occurs in many biological interactions [4–7]. Examples of theses interactions are those which occur between an antibody and antigen, enzyme and substrate, or hormone and receptor [1–5]. Affinity chromatography makes use of these systems by immobilizing one of the pair of interacting agents onto a chromatographic support. The agent that is immobilized onto the support is known as the “affinity ligand” and provides a column with the ability to selectively retain the complementary target even when this compound is present in a complex mixture [4–6].

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The simplest and most common format for affinity chromatography is the on/off mode, as shown in Figure 1 [4,8]. In this format, an application buffer is used to first pass the sample onto a column that can capture and retain the target. The application buffer usually mimics the pH and ionic strength at which the affinity ligand is fully active and has its strongest binding to the target [6,8]. In the presence of the application buffer, the target is retained while other sample components are eluted with little or no binding. A strong mobile phase, or elution buffer, is then passed through the column to release the target for collection or analysis. The elution buffer may be applied by using a step change or gradient [8]. Release of the target by changing the pH, ionic strength, or mobile phase composition is known as non-specific elution [4,8]. An alternative approach for elution is to employ a competing agent which displaces the target by means of mass action (i.e., biospecific elution) [4,6,8]. Once the target has been released from the column, the system can be re-equilibrated with the application buffer, and the process is repeated [8]. In some cases, the application and elution buffers may be the same solution, giving a method that is carried out under isocratic conditions [8–10]. This last situation occurs in the method of weak affinity chromatography (WAC), which uses affinity ligands that have weak-to-moderate binding strengths for their targets (i.e., association equilibrium constants of less than 10^5-10^6 M^{-1}) [1,6,8–10].

The selectivity and simplicity of affinity chromatography have made this method useful in the purification of many biomolecules, biopharmaceuticals, and other agents [1–6]. Affinity chromatography has been used for both sample preparation and as an analytical tool for the isolation or measurement of specific targets in biological, clinical and environmental samples [1–5]. In addition, this method has been utilized as a tool to study and characterize biological interactions [1,11–15]. This review will discuss the history and development of affinity chromatography and look at how this field has developed over the last five decades. This discussion will include a consideration of the types of supports, immobilization methods, affinity ligands, and separation formats that have been used in this field. Both traditional and newer applications of affinity chromatography will also be examined.

2. Origins of affinity chromatography

The concept of utilizing immobilized biological agents to isolate specific targets dates back to the beginning of the 20th century [7,16,17]. The first reported use of this approach was in 1910 by Emil Starkenstein [16,18], only a few years after the development of column liquid chromatography by Michael Tswett [19]. Starkenstein exploited the binding that occurs between an enzyme and its substrate when he purified α-amylase by using insoluble starch as both the stationary phase and support for his separation [7,16,18]. Several additional studies were conducted in the 1920s through 1940s by utilizing this general approach to isolate amylase and related enzymes [16,20–23]. The same principle of using an immobilized substrate for enzyme purification was adopted for the enrichment of lipase by using powdered stearic acid, the purification of pepsin by employing edestin (a crystalline protein), and the isolation of porcine elastase by using powdered elastin [24–27].

Around the same period of time, chromatographic separations based on biological interactions were extended to the purification of antibodies [16]. Initial studies in the mid-1930s used supports like charcoal and kaolin with adsorbed antigens for antibody

purification [28,29]. The diazo coupling method was used by Landsteiner and van der Scheer in 1936 to couple haptens to chicken erythrocyte stroma, which were then used to isolate antibodies that could bind to these haptens [30]. Covalent immobilization was extended to other supports by Campbell et al. in 1951; in their study they isolated rabbit antibodies to bovine serum albumin (BSA) by employing BSA that was coupled to diazotized *p*-aminobenzyl-cellulose [31]. Variations of this technique were used with immobilized haptens for antibody purification [32] or with immobilized substrate analogs or inhibitors for enzyme purification [17]. Examples of the latter application included the purification of mushroom tyrosinase on *p*-azophenol-substituted cellulose [33] and the isolation of liver flavokinase or other flavin mononucleotide (FMN)-dependent enzymes on flavin-substituted celluloses [34,35]. Cellulose derivatives were further applied to the purification of specific strands of nucleic acids [36], transfer RNA [37] and nucleotides [38].

The next set of major advances in supports and immobilization methods occurred in the 1960s. One of these advances was the creation of beaded agarose as a support [7,16]. This support avoided many of the issues with mechanical stability that occurred with cellulose-based supports in liquid chromatography [39]. A second major advance was the development of the cyanogen bromide (CNBr) immobilization method [40]. This method offered a relatively easy means for attaching peptides and proteins through non-protonated amine groups to CNBr-activated agarose [17]. These two advances were combined in 1968 by Cuatrecasas, Anfinsen, and Wilchek for the immobilization of nuclease inhibitors to beaded agarose, which was then used for nuclease purification [41]. The resulting paper was the first time the name “affinity chromatography” was given to a method that used a biological agent in a column as a specific means for target separation or isolation [41].

Affinity chromatography has become a common tool in biochemical and chemical separations over the last 50 years [1–7]. The growth of this method is illustrated in Figure 2 by the number of publications that have appeared each year since 1968 and which contained the term “affinity chromatography”. A similar trend, with almost double the number of papers, is seen when a search is made of publications that included either the name or concept of affinity chromatography (see Supplementary Material). The two decades from 1968 to 1990 saw a rapid, steady increase in the number of publications in this field. This field has remained quite active even over the last three decades. There are now over 50,000 papers that have contained the term “affinity chromatography” and more than 122,000 papers that have used or mentioned this method.

3. Supports in affinity chromatography

Various materials and matrices have been used as supports in affinity chromatography. Examples of these supports, and an indication of their relative extent of use, are given in Figure 3. Agarose has remained a popular support for affinity chromatography since the work by Cuatrecasas et al. in 1968 [41]. Advantages of using agarose as a support for affinity chromatography are its low cost, its large pore size (e.g., for biomolecule separations or immobilization), its low non-specific binding for many biological agents, and its good stability over a broad pH range [42]. These features have made agarose a common material in affinity chromatography for both the large- and small-scale purification of targets, as

indicated in Figure 3 [42–44]. However, agarose has limited mechanical stability at high operating pressures. This last factor tends to limit the use of agarose as a support in analytical-scale separations based on high performance liquid chromatography (HPLC) [4,10,45–47].

Other types of carbohydrates have also been employed as supports in affinity chromatography [42]. As indicated in Figure 3, one important example is cellulose. Cellulose was commonly used in early applications of affinity chromatography that appeared for antibody or enzyme purification in the 1950s and 1960s [31,33–35]. Although cellulose is currently not as popular as agarose for many applications of affinity chromatography, this material is often used in membrane-based affinity separations [42,48]. Despite having a low surface area and lower mechanical stability than beaded agarose, cellulose in a membrane format can provide a low backpressure and be used in preparative work at high flow rates [42,49]. Carbohydrate-based supports have also been used in hybrid materials with a dense core (e.g., quartz), as utilized in expanded-bed adsorbents [42]. These latter supports help avoid column clogging due to solid contaminants by allowing the creation of a fluidized or expanded bed during sample application [42,50].

Work in the late 1970s and early 1980s began to explore supports that could be used to combine affinity chromatography with HPLC [4,10,45–47]. This combination has been referred to as high-performance affinity chromatography (HPAC) or high-performance liquid affinity chromatography (HPLAC) [4,10,42,45]. Porous silica particles, or glass beads, that had been modified to contain hydrophilic groups (e.g., diols) soon began to see common use in HPAC [4,10,45–47,51,52]. Advantages offered by these materials are their availability in a variety of pore sizes and particle diameters, their good mechanical strength under the conditions used in HPLC systems, their ability to be modified for the immobilization of a wide range of affinity ligands, and their compatibility with applications that spanned from target purification to pharmaceutical or biomedical analysis and flow-based immunoassays [4,10,45–47,51–53]. Disadvantages of silica and glass-based supports include their lower range of pH stability and higher non-specific binding in their non-modified forms when compared to many carbohydrate supports [42].

A variety of organic polymers have also been used as supports for affinity chromatography. Many of these organic polymers have been based on polystyrene or polymethacrylate [42]. Native polystyrene has a hydrophobic backbone which could lead to high levels of non-specific interactions in affinity chromatography. However, hydrophilic coatings can be placed on this material, thus allowing use of polystyrene supports for affinity chromatography based on perfusion media or other separation formats [42,54,55]. Polymethacrylates are more hydrophilic in nature and can be used in either their original or modified forms for affinity separations [56,57]. Organic polymers based on coated polystyrene or polymethacrylates have been used in HPAC [42,51,52]. Other examples of organic polymers that have been used in affinity chromatography are polysulfones and polyamides, which have been employed in membrane supports [48,49]. Like agarose, many of these organic polymers can be used over a large pH range and have good biocompatibility [42,44].

One area of growth in affinity chromatography over the last 15-20 years has been in the creation and use of monolith supports [4,42,51,52]. Originally developed in the 1990s for other forms of chromatography, monolith supports offer several advantages over traditional particulate supports [4,51,52]. These advantages include their low backpressures, high permeability, good separation efficiencies, and ability to be made in a variety of sizes and shapes [4,58–60]. There are several types of monoliths that have been employed in affinity chromatography, ranging from organic polymers to silica, agarose, and cryogels [59–63]. Many monoliths that have been used in affinity chromatography are polymers based on glycidyl methacrylate (GMA) and ethylene glycol dimethacrylate (EDMA), which have been used with immobilized agents that include antibodies, enzymes, and peptides [42,58,61–63]. This includes polymethacrylate monoliths known as convective interaction media (CIM), which have been employed in applications that range from the purification of large biological agents (e.g., DNA, proteins, and viruses) [60] to antibody-based separations [64,65] and immobilized metal-ion affinity chromatography (IMAC) [66–69].

Other alternative materials have been explored in recent years as supports for affinity chromatography. One of these materials is titania (TiO_2) [70–75]. Titania-based supports have been mostly used for the isolation of phosphopeptides in a method that has been referred to as metal oxide affinity chromatography (MOAC) [70–73]. Titania nanoparticles and dendritic polyglycerol-coated chitosan nanomaterials containing Ti^{4+} have also been employed in IMAC for the separation and purification of phosphopeptides and glycopeptides [74,75].

There are many ways in which supports may be employed in affinity chromatography, as demonstrated in Figure 4. A packed column is the most common of these formats. This is not surprising given this approach was used in the early work with affinity chromatography, spanning from the studies by Starkenstein in 1910 [16,18] through the beginning of the modern era of affinity chromatography in 1968 [41]. As shown in Figure 4, packed columns have remained the main support format in affinity chromatography, being utilized in more than 90% of the reported applications in this field over the last 50 years. This has included both work with low-to-medium performance supports like agarose or cellulose and supports for HPAC, such as silica or glass beads [4,10,42–45].

Several other support formats can also be employed in affinity chromatography [42]. Capillary supports have been used with affinity ligands since the early 1980s and, as shown in Figure 4, represent the second most popular format over the last 50 years [76,77]. Monoliths and perfusion-based media, which both contain flow-through pores to aid in mass transfer, have grown in popularity over the last two decades for analytical and preparative applications of affinity chromatography [4,42,51,52]. Expanded or fluidized beds have mainly been utilized over the last 20-30 years for preparative uses of affinity chromatography, as have membranes and fiber-based supports [42,48,49]. In addition, a growing number of reports over the last 15-20 years have used several of these support formats (e.g., capillaries, packed beds and monoliths) in microchips and miniaturized devices for sample preparation or analysis [76–78].

4. Immobilization techniques in affinity chromatography

As was noted earlier, the availability of suitable immobilization methods has long been linked to the development of new applications for affinity chromatography. Figure 5 shows various schemes that can be used for immobilization. The correct selection of an immobilization scheme is still a crucial factor to consider when preparing an affinity column [1,43,79,80]. This choice can have a profound impact on the final activity of the affinity ligand. For instance, improper orientation and steric hindrance that result from immobilization can lead to a decrease in the actual or apparent activity of a binding agent. Multisite attachment of an affinity ligand to the support can also lead to an alteration in a binding agent's activity [80].

Covalent immobilization, as initially employed in 1936 by Landsteiner and van der Scheer [30] and in 1951 by Campbell et al. [31], remains the most frequently used means for placing an affinity ligand on a support [79,80]. Activation of the support and/or ligand is usually a prerequisite for this approach. In the cyanogen bromide (CNBr) method, as used by Cautrecasas et al. [41], hydroxyl groups on the support are first modified to form an active cyanate ester or imidocarbonate group; these groups can react with primary amines on an affinity ligand to form an isourea linkage [43,80]. Binding agents can also be immobilized through amines by using surfaces that are activated with carbonyldiimidazole or *N*-hydroxysuccinimide [43,80–83]. Another covalent coupling that can be used with amine-containing agents is reductive amination, or the Schiff base method [80]. Binding agents containing hydroxyl or carboxyl groups can be used in covalent immobilization as well [43,80,84].

Improper orientation or multisite attachment that is created by ligand coupling through relatively common groups, such as amines, can be avoided by utilizing alternate and more site-selective sites on a ligand for immobilization [80]. Several methods, for example, are available for coupling proteins to supports through free sulfhydryl groups [43,80,84–86]. Carbohydrate groups, which are found in specific locations on antibodies or other glycoproteins, can also be used for covalent immobilization [43,80,87–92]. The carbohydrate groups are usually first oxidized with periodate or converted through enzymatic treatment to form aldehyde groups [80,87,91]. Ligand attachment is then accomplished by reacting the aldehydes with a support that contains amines or hydrazide groups [88–91].

Affinity ligands can also be placed on a support through methods other than covalent attachment [1]. Early work in the field of affinity chromatography made use of non-covalent immobilization [18–29]. This approach is based on the physical adsorption of a binding agent onto a surface through forces such as electrostatic interactions, hydrophobic interactions, or hydrogen bonding [79,80]. The type of interaction that is used for immobilization will depend on the support and affinity ligand. Both carbohydrates and inorganic supports (e.g., alumina and silica) have been used for non-covalent immobilization [80,93–97]. A major advantage of this approach is its simplicity [80,97]. Disadvantages include the possibility of limited stability for an affinity support that is prepared through

non-covalent immobilization and the loss of binding agent activity through random orientation [80].

Biospecific adsorption is a form of non-covalent immobilization that employs a secondary ligand that is attached to a support for binding and immobilizing the primary affinity ligand [1,80,84]. An early example of this approach appeared in 1976 when peptides and proteins were modified with biotin tags and coupled to supports that contained immobilized avidin [98]. The same method can be used with biotin tags and supports that contain streptavidin [43,80,84,99,100]. Another example of biospecific adsorption that often appears in the literature is when protein A or protein G (i.e., immunoglobulin-binding proteins) is used on a support to bind and immobilize antibodies [1,80,100,101].

Another set of non-covalent immobilization methods are those based on encapsulation or entrapment [80,102–108]. Early work in this field accomplished this type of immobilization by forming an organic polymer around the affinity ligand [103,104]. Inorganic materials created with silicate-based sol gels have received particular attention for many years in the entrapment of enzymes, proteins and other affinity ligands [105–108]. As an alternative, an affinity ligand can be placed on or within a support and entrapped through cross-linking or changing the ligand's ability to leave this material [80,109–113] For instance, the protein BSA has entrapped through cross-linking this protein with glutaraldehyde [109]. In addition, human serum albumin (HSA), alpha$_1$-acid glycoprotein (AGP), IgG, and other agents have been recently entrapped within silica by using hydrazide-activated supports and oxidized glycogen as a capping agent [110–113].

An alternative approach to immobilization in affinity chromatography is to use molecular imprinting [114–118]. This method appeared in the early 1970s for use in chiral separations [119]; however, it is also now often used in solid-phase extraction and chromatographic methods [114–118]. The general goal in this method is to create a support with binding pockets that act as affinity ligands for the desired target [117,118]. One way of making a molecularly imprinted polymer (MIP) is to mix the target with a polymerization mixture that contains monomers with functional groups that can interact with the target. The target is then washed from the polymer, giving a support with cavities or pockets that be used to bind the same type of target in applied samples [114–118]. The interactions exhibited by MIPs are similar to those in biological systems and have been used in many past studies for the binding and isolation of many low-mass targets [115–118]. More recent work has explored the development and use of MIPs with macromolecules such as proteins [120–122]. MIPs have been used with both particulate supports and monoliths for selective retention in solid-phase extraction and affinity chromatography [114–118,123–125].

5. Binding agents in affinity chromatography

One way of categorizing the various types of affinity chromatography is by the type of binding agent that is used for the separation [1–5]. Many binding agents have been utilized as stationary phases in affinity chromatography. As shown in Figure 6, this method has made use of both naturally-occurring binding agents and non-biological ligands [1–5,100,114–118,126–131]. Natural binding agents employed in affinity chromatography have included

enzymes, antibodies, antigens, immunoglobulin-binding proteins, biotin plus avidin or streptavidin, lectins, serum proteins, carbohydrates, lipids, and nucleic acids [1–5,84,100]. Non-biological ligands have included aptamers, dyes, metal ion chelates, MIPs, and boronates [1,114–118,126–131].

5.1. Biological binding agents

The use of a naturally-occurring, biological binding agent in an affinity column is often referred to as bioaffinity chromatography or biospecific adsorption [1,4,84,100]. This is the type of chromatography that was first described by Starkenstein in 1910, in which starch was used as an immobilized substrate to isolate the enzyme α-amylase [18]. This is also the type of affinity chromatography that was used in most of the early work in this field for enzyme and antibody isolation [16] and by Cuatrecasas et. al. in 1968 for staphylococcal nuclease, α-chymotrypsin and carboxypeptidase A on columns that contained immobilized nuclease inhibitors [41]. Bioaffinity chromatography has remained one of the most common forms of affinity chromatography over the last five decades [1,4,16,84,100].

The use of affinity chromatography to isolate enzymes has remained an important application for this technique [1–5,100,132]. Non-biological agents such as dyes are now often used for this application [126,127], but some biological agents are still used for enzyme separation and isolation, including immobilized inhibitors, substrates, and cofactors [1–5,10,132–134]. Enzymes can also be immobilized in affinity columns for the separation of inhibitors and other solutes [10,135]. Penicillin G acylase, glucoamylases G1 and G2, cellobiohydrolase I, trypsin, α-chymotrypsin, lysozyme, and pepsin have been employed in affinity chromatography for the separation of various drugs, inhibitors and other solutes that bind to these enzymes [10,132,135–142].

Immunoaffinity chromatography (IAC) is by far the most common form of bioaffinity chromatography, as demonstrated in Figure 6 [101,144–146]. In this approach, the binding of an antibody with its corresponding target, or antigen, is used as the basis for the affinity separation. Antibody-antigen interactions are strong and highly selective and can involve many types of compounds as the antigen [144–152]. These properties have long made IAC a popular and powerful tool for the capture and isolation of specific targets from complex samples. Early examples in which immobilized antigens were used to purify antibodies include the work by D'Allesandro and Sofia in 1935 [28], by Landsteiner and coworkers in 1936 [30], and by Campbell et al. in 1951 [31]. In 1971, Wilchek and co-workers reported the use of antibodies attached to an agarose support for the isolation of modified peptides [149]. IAC methods that have since been reported for a large array of targets that span from hormones and toxins to peptides, antibodies, enzymes, recombinant proteins, and viruses [144–148,150–153]. The same properties that have made IAC valuable as a purification tool have also made it attractive as a means for sample preparation and analysis [144–146,154–156]. Examples of these latter applications will be discussed in Section 6.

Immunoglobulin-binding proteins are a third class of biological binding agents that are often used in affinity chromatography [100,101,157–167]. As indicated by Figure 6, this combination is the second most-reported form of bioaffinity chromatography. Two examples that were discussed in Section 4 with regards to biospecific adsorption are protein A and

protein G [1,80,100,101]. Protein A is a bacterial cell wall protein from *Staphylococcus aureus*; it is commonly employed in the detection or purification of many subclasses of immunoglobulins from various species [100,101,157–159]. Protein G is produced by group G Streptococci and can have different selectivity than protein A for some immunoglobulin subclasses and species [100,101,160]. Protein L is another binding agent in this group; this agent is derived from *Peptostreptococcus magnus* and has strong binding with human IgG and IgA [162,163]. Mixtures of immunoglobulin-binding proteins or recombinant forms such as protein A/G and protein G/L have also been used in affinity methods [100,101]. These immunoglobulin-binding proteins can be used to capture and purify antibodies, as well as to measure immunoglobulins in samples [100,101,157–167].

Another form of bioaffinity chromatography is based on the interactions of biotin with proteins such as avidin and streptavidin for immobilization or to carry out separations [43,80,84,99,100]. Biotin is also known as vitamin H or vitamin B_7 [99,100,168]. Streptavidin is produced by *Streptomyces avidinii*, while avidin is a glycoprotein found in egg whites [100,169,170]. Both avidin and streptavidin exhibit strong binding towards biotin and have association equilibrium constants in the range of 10^{13} to 10^{15} M^{-1} for this binding [99,100]. A common example of these type of interactions is used to capture a biotinylated target on a streptavidin or avidin support, as was demonstrated for biotin-labeled peptides and proteins in the mid-1970s [98]. Avidin has recently been used with biotin and affinity columns in various formats to isolate proteins under native elution conditions [171]. Streptavidin-biotin interactions have also been employed in miniaturized affinity systems to identify and characterize ligands for nanodisc-embedded G-protein coupled receptors [172].

Lectins are another group of binding agents that are often used in bioaffinity chromatography [100,173–177]. The resulting method is sometimes known as lectin affinity chromatography (LAC) [100,175]. Lectins are non-immune system carbohydrate-binding proteins that are capable of binding reversibly to targets that contain sugar moieties [100,173,174]. A common example of a lectin that is often used as a support in affinity chromatography is concanavalin A (Con A). This lectin binds to high-mannose type glycans and glycans with mannose branching [100]. Wheat germ agglutinin (WGA) is another type of lectin that has been employed as an affinity ligand in chromatography. It is able to bind to N-acetyl-D-glucosamine and sialic acid [100]. Recent work has used serial lectin affinity chromatography, in which lectin columns are coupled together, to characterize glycans on the same glycoconjugate by arranging the columns in various orders [175]. There have also been studies in which lectins have been used with monolith supports containing immobilized Con A and WGA [176] and affinity microcolumns that contain Con A or *Aleuria Anrantia* lectin (AAL) [177].

Serum proteins have been used as binding agents in many reports employing bioaffmity chromatography [12,100]. Two examples are the transport proteins BSA and HSA [12,100,143,178]. These are the most abundant proteins in bovine and human plasma, respectively, and have weak-to-high strength interactions with a variety of drugs, hormones, and fatty acids [12,178–180]. Another example of a serum protein that has often been used in bioaffmity chromatography is AGP [100,143,179,180]. AGP is an acute phase protein with a high carbohydrate content that binds to many basic, neutral, and cationic drugs

[100,143,179]. Each of these serum proteins has been used as a chiral stationary phase and to study how factors such as solute structure, temperature, and composition or pH of the mobile phase affect the resulting chiral separations [179–185]. Columns containing these transport proteins have also been employed to examine the affinities and binding sites of numerous drugs with these proteins, as well as to characterize allosteric interactions and the effects of protein modifications on drug binding [180–188]. In addition, affinity microcolumns containing serum transport proteins have recently been used in the method of ultrafast affinity extraction to characterize drug interactions with soluble binding agents [15,189–193].

Carbohydrate-based ligands have also been employed in bioaffmity chromatography [100]. Some examples are the use of amylose, cellulose, and their derivatives for chiral drug separations [194–196]. The carbohydrates α-, β-, and γ-cyclodextrin have also been frequently used in chiral separations. This latter group of carbohydrates are composed of 6-to-8 glucopyranose units that are arranged in a circular polymer with a hydrophobic cavity and a hydrophilic exterior [100,197,198]. Chiral selection of a drug can occur with these binding agents through the formation of an inclusion complex with hydrophobic cavity of cyclodextrin and differential binding of the drug solute to groups located at the mouth of the cavity [100,199]. Cyclofructans, which are macrocyclic oligosaccharides based on D-fructofuranose, are another group of carbohydrates that have been employed as stationary phases for chiral separations [200].

Lipids are another class of biological agents that have been employed in bioaffinity chromatography [10,201]. For instance, lipids have been used in immobilized artificial membrane (IAM) chromatography to determine the partition coefficients of drugs for cell membranes [202]. Monolayers of phospholipid analogs such as phosphatidyl choline, sphingomyelin, and choline have all been used as biological ligands in this method [203–205]. IAM has been employed for examining drug interactions with immobilized receptors and transporters [206–210]. In the method of immobilized liposome chromatography (ILC), liposomes or lipid bilayers have been placed on chromatographic supports and utilized to study drug-membrane interactions [211–219]. ILC has been utilized to screen membrane penetrable components and bioactive ingredients in traditional medicine [211–215]. Lipids such as phosphatidylcholine and cholesterol have been also immobilized on monolithic supports for use in IAM or related applications [220–222].

Nucleic acids can also be used as ligands for bioaffinity chromatography [223–232]. This is the case in DNA affinity chromatography, which is a technique used to retain and purify DNA-binding proteins [223–230] (Note: the related field of aptamer affinity chromatography is discussed in Section 5.2). This method first appeared in the late 1960s and early 1970s [225–228]. DNA-binding proteins that have been isolated by this approach include DNA or RNA polymerases, DNA repair proteins, helicases, histones, primases, restriction enzymes, teleomerases, topoisomerases, and transcription factors [223–227,231,232]. In non-specific DNA affinity chromatography, a general preparation of fragmented nuclear DNA (e.g., calf thymus DNA) is used in a column to separate DNA-binding proteins from other proteins and sample components that do not bind DNA [223]. In specific DNA affinity chromatography, a particular section of DNA is used as the affinity

ligand. The ligand in this case is chosen to have a sequence, structure, or restriction site that can be used to capture a protein that will interact specifically with this DNA segment [223,232].

5.2 Non-biological binding agents

The use of non-biological agents in affinity chromatography began in the early 1970s, soon after the emergence of modern affinity chromatography. One area that appeared during this time was dye-ligand affinity chromatography [126,127]. In 1971 Staal et. al. used the dye Blue Dextran as a binding agent in an affinity column to isolate pyruvate kinase [233], following the observation that this dye co-eluted in a soluble form with pyruvate kinase on a gel filtration column [234]. Most of the binding agents used in this method are triazine dyes or related compounds [126,127,235]. These dye-ligands contain a chromophore and reactive group for a covalent coupling to a support. Chromophores that are present on these dyes, and which are used for dye-protein binding, have included anthraquinone, azo, and phathalocyanine groups [126,127,235]. Further modifications to the structures of these dyes have been made over the years to improve their specificity in interacting with a given target [127,235,236]. The low cost, ease of immobilization onto supports, and stability of dye-ligands have made these binding agents popular in affinity separations, as demonstrated in Figure 6, and especially for large-scale processes [126,127]. Examples of proteins that have been purified through the use of dye-ligands are HSA, lysozyme, fucoidan, lactoferrin, α-chymotrypsin, and IgG [126,127,235–244].

Dye-ligand affinity chromatography is part of a broader range of methods known as biomimetic affinity chromatography [127,243,244]. This area includes the use of dyes as ligands along with binding agents that are produced by means of combinatorial synthesis or selection from large libraries of potential affinity ligands (e.g., using phage display or ribosome display techniques) [127]. Aptamers are important example of binding agents that are developed through the screening of libraries containing potential ligand candidates [127,245]. Aptamers are synthetic oligonucleotide sequences, generally based on DNA or RNA, that are screened and chosen for their binding to specific target molecules [127,245]. Aptamers have been popularized through the availability of a screening and amplification method known as the systematic evolution of ligands by exponential enrichment (SELEX), which was first reported in 1990 [246–248]. The three-dimensional structure of an aptamer can lead to relatively strong and specific non-covalent complexes with its binding target [127,245,248–250]. Aptamers have been used in a number of studies as alternatives to antibodies due to the good specificity of aptamers, their low immunogenicity, and their ability to be produced without the need for a biological system [245,248–250]. Applications of aptamers in affinity chromatography have included their use to bind small molecules such as ochratoxin A, cocaine, and diclofenac; aptamers have also been used to bind larger targets such as proteins and cells [251–264]. Aptamers have been immobilized onto both organic and inorganic supports, including monoliths, and have been used in various formats that range from columns to microfluidic systems [127,256–264].

As discussed in Section 4, MIPs are a group of polymeric supports that are prepared to contain cavities or pockets that can bind to given target [114–118,265]. Affinity-based

applications for this type of support include chiral separations and solid-phase extraction [114–119,265–271]. Reports in which MIPs are used in some form with chromatography, including as tools for sample preparation, now make up one of the three main groups of affinity applications that employ non-biological binding agents (see Figure 6). Target compounds for these supports are often low-mass solutes [115–118,265]. However, methods are also now available for the use of MIPs with large targets like proteins [120–122]. Most of the early work with MIPs made use of organic polymers to create this type of medium, but other materials such as monoliths, hybrid materials, and membrane-based MIPs have also been reported [114–118,123–125,265,272–275].

As shown in Figure 6, metal ion chelates are another important example of non-biological binding agents that can be used in affinity chromatography. This combination is the basis of the method of IMAC [66–69], which was briefly introduced in Section 4. In 1975, Porath et. al. published the first application of IMAC, in which this method was demonstrated through its use in the purification of albumin [128]. IMAC generally relies on the interaction between immobilized metal ions and amino acids on the target analyte that can act as electron-donating groups, such as cysteine, histidine, or tryptophan residues [129–131]. Iminodiacetic acid, nitrilotriacetic acid, carboxymethylated aspartic acid, diethylene triamine pentaacetate, and tris(carboxymethyl) ethylene-diamine are examples of chelating ligands that have been used in IMAC to contain metal ions [129,131,276,277]. These chelating ligands have been immobilized onto several types of supports, including silica, agarose, and cryogels [129–131,276–278]. Various metal ions have also been used in IMAC [129–131]. Metal ions such as Cu^{+}, Ag^{+}, Pd^{2+}, Pt^{2+}, Cd^{2+}, and Hg^{2+} tend to bind targets that contain sulfur, while metal ions such as Ni^{2+}, Cu^{2+}, and Zn^{2+} tend to coordinate with targets having accessible groups that contain nitrogen, sulfur, or oxygen [131,279–281]. Protein purification is a common use of IMAC [131,282,283]. For instance, this method has been employed in purifying natural proteins such as HSA, immunoglobulins, lysozyme, and α-amylase [129–131,276,283]. IMAC has also been used to isolate histidine-tagged recombinant proteins, DNA-based aptamers, and phosphopeptides [131,278,282,284,285].

Boronic acid and its derivatives represent another class of non-biological binding agents that have been utilized in affinity chromatography [286–289]. This combination is known as boronate affinity chromatography (BAC) [287–289]. Boronate affinity chromatography was first described in 1970, when it was used to retain various nucleosides and sugars [290]. This method has since been used for the separation of compounds that contain cis-diol groups, such as glycoproteins, catechols, nucleotides, and carbohydrates [286–289]. For instance, BAC supports have been used to enrich glycoproteins and glycopeptides from tryptic digests of horseradish peroxidase and human serum and nucleosides in urine samples [291–296]. Esterification is the main reaction that occurs between the boronic acid moiety and cis-diols; this reaction is reversible and is affected by pH [287–289]. The boronate/cis-diol complex that is formed is hydrolyzed and undergoes dissociation under acidic conditions or when the pH is far lower than the pK_a of the boronic acid. This property allows BAC to be used with the pH-controlled capture and release of cis-diol compounds [286–289]. Common binding agents that are used in BAC are 3-aminophenylboronic acid and 4-vinylphenylboronic acid, which have pK_a values of 8.8 and 8.2, respectively. Other binding agents have also been

developed for BAC with lower pK_a values, thus producing boronates that can bind to their targets in more neutral or acidic samples [289,297–300].

6. Applications of modern affinity chromatography

There are many ways in which affinity chromatography can be used for chemical or biochemical separations, purification, analysis, or characterization. Figure 7 shows some fields in which affinity chromatography has been used on a frequent basis, based on research publications that have used this method. Many of these applications have been in the fields of biochemistry, biochemical research and molecular biology (a combined total of 49.2% for the papers examined in Figure 7). This is not surprising in that the affinity chromatography was originally developed to meet the need for specific separations in these fields [16,20–38,41]. In a similar manner the areas of biotechnology, microbiology, cell biology, and immunology also employ this separation method on a routine basis (combined total of 22.7%) [47,48,120,131,223,301,302]. Analytical chemistry and other areas of chemistry (e.g., environmental chemistry, clinical chemistry, multidisciplinary chemistry) make up another important set of applications for affinity chromatography (17.7%) along with pharmacology and pharmaceutical science (4.2%). These applications emerged in the early 1970s and saw rapid growth after the development of high-performance affinity methods in the late 1970s and early 1980s [10,12,45,46,145,153,303–307]. The use of affinity chromatography in biophysical studies of biological systems (4.2%) is another consistent area of applications, with work based on this combination first appearing in the mid-1970s [11–15].

Many of the applications that are represented by Figure 7 involve the use of affinity chromatography as a method for the purification of biomolecules [1–7]. This is not surprising given the history behind the development of this method, as discussed in Section 2. This type of application makes use of the ability of affinity chromatography to provide both high selectivity and strong binding for a given target, making it possible to often isolate this target in only one or a few steps even when it is present in a complex matrix [1–6]. Important examples of these applications are the use of affinity chromatography for both the small-scale and large-scale purification of enzymes, native proteins, and recombinant proteins, such as by using dye-ligand or biomimetic affinity chromatography [1–7,126,127,132,243,244,301]. Common examples of popular small-scale applications are the isolation of his-tag proteins by IMAC, and the isolation of specific antibodies or antigens by IAC [100,101,129–131,144,146,302].

Cell affinity chromatography is another important application involving target purification by affinity-based separations [308–327]. In this area, affinity chromatography is used to isolate or separate certain types of cells by using interactions between agents on the surface of the cell (e.g., receptors or glycoproteins) and ligands that bind these agents [308–310]. Examples of affinity ligands that have been used for this purpose are lectins, which can interact with glycoproteins on cell membranes, and antibodies, which can bind to specific surface proteins [308,309]. Work in this area began in the early-to-mid 1970s, when insulin receptors from liver cell membranes were purified by affinity chromatography [311] and tumor cells with high immunogenicity were isolated by using Con A as a binding agent

[312]. Cell affinity chromatography has also been utilized to isolate thymocytes, red blood cells, platelets, lymphocytes, granulocytes, spermatozoa, cancer cells, and antimicrobial peptides [311–320,322,324,325,327]. Cell affinity chromatography has been employed in various formats, including columns, capillaries, microarrays, magnetically stabilized fluidized beds, microfluidic devices, cryogels, and monoliths [308–327].

Over the last four decades, affinity chromatography has also become an important analytical tool. As mentioned earlier, this trend largely followed the development of high-performance techniques based on affinity chromatography that are suitable for use in HPLC systems [10,12,45,46,145,154,303–307]. The on/off elution mode of affinity chromatography, as illustrated earlier in Figure 1, is often used in these applications due to simplicity, speed, and ease of automation [4,52,53,154]. Analytical methods based on antibodies or antigens, protein A or protein G chromatography, IMAC, boronates, and lectins have all been reported based on this approach [303,304,306]. Target compounds with moderate concentration can often be detected directly in these methods by using online fluorescence or absorbance detectors, as well as by using mass spectrometry or postcolumn reaction schemes [52,144,146,154]. In addition, affinity columns have been combined with other analysis methods such as reversed-phase chromatography, gas chromatography, and capillary electrophoresis to provide multi-dimensional techniques for the separation and/or analysis of chemicals in samples [154]. Indirect detection of a target analyte can also be used with affinity columns. This approach is frequently used with affinity columns in the area of chromatographic immunoassays [144,154–156,307]. For instance, a labeled analog of the target may be used to compete with the target or to be displaced by the target from a column that contains immobilized antibodies that can bind to either of these agents [144,154,156, 328–330]. Alternatively, antibody- or antigen-containing columns can be used with labeled agents in chromatographic immunoassays that employ sandwich or one-site immunometric assays to measure a given target [154,156,331–333].

Affinity chromatography is frequently used in analytical methods as a means for sample pretreatment [10,12,154,303,304,306]. For instance, MIPs are often used in solid-phase extraction [265,267]. Another common example is immunoextraction, in which an affinity column that contains immobilized antibodies is used to capture one or more target solutes prior to their analysis by another method [146,154,156]. This latter method has been coupled on-line and off-line to liquid chromatography, capillary electrophoresis, and mass spectrometry, as well as off-line with gas chromatography [154,156]. Another use of affinity chromatography for sample pretreatment is to selectively remove one or more components from a sample before other solutes in the same sample are further processed and measured [334]. This situation occurs in the technique of immunodepletion, which is now often used in proteomics and employs immobilized antibodies to remove high-abundance proteins from samples prior to the analysis of low-abundance proteins [334–337].

Another analytical application for affinity chromatography is in chiral separations [143,179,338–341]. Chiral stationary phases (CSPs) were first employed for chromatographic separations in the late 1970s and are now important tools for drug discovery and development [143,179,341]. Examples of chiral stationary phases that were already mentioned in Sections 4 and 5 were MIPs [114–119]; serum proteins such as BSA,

HSA, or AGP [179–184]; and carbohydrate phases based on amylose, cellulose, cyclodextrins, or cyclofructans [100,194–196,199,200]. Other agents that have been used as CSPs are enzymes such as cellobiohydrolases, α-chymotrypsin, penicillin G acylase, and lysozyme; streptavidin or avidin; ovomucoid; and antibodies [143,180,338–341].

A final way in which affinity chromatography can be utilized is to examine biological interactions [11–15]. One way this method can be employed is to characterize the binding strength of such an interaction and the number or types of sites that are involved in this process [11,13,77,180,187–190,303]. Affinity chromatography has been used for this purpose since the early 1970s and has been employed for examining a large number of interactions, including protein-protein, drug-protein, enzyme-inhibitor, antibody-antigen, aptamer-target and receptor-ligand interactions, among others [11–15,305]. One common approach for this work is zonal elution, which is a method in which the retention or peak of an analyte is examined as this analyte is injected onto an affinity column that contains an immobilized binding agent; the mobile phase in this case may also contain an additive or competing agent [11–13]. This technique can provide data on the binding strength of the affinity ligand with an injected analyte or mobile phase additive and on the types of interactions that are present between these agents (e.g., the number of common binding sites in the system and whether direct competition or allosteric effects are present) [13]. A second method that is often used in affinity chromatography for binding studies is frontal analysis [11–13]. Frontal analysis is performed by continuously applying a known concentration of the analyte onto the affinity column until a front, or breakthrough curve, is formed. The position and shape of the breakthrough curve can then be used to determine the equilibrium constants and number of binding sites of the applied analyte for the affinity ligand [13].

Affinity chromatography can also be employed to examine the kinetics of a biological interaction [11,13,15,342,343]. A number of methods have been created for this work since the mid-1970s, including techniques based on band-broadening measurements, peak-fitting methods, the split peak effect, and peak decay analysis [15,180,190–193,342,343]. These approaches have been used to examine a variety of biological systems that include protein-protein, drug-protein, antibody-antigen, aptamer-target interactions [15,180,342,343]. Another method based on affinity chromatography that has appeared more recently is ultrafast affinity extraction, which has been used to study the binding and dissociation of drug-protein complexes. This method uses an immobilized binding agent in a microscale affinity column to extract the non-bound form of a drug in an injected sample in the second-to-millisecond time domain [190–193,345–347]. By varying the time that is allowed for this extraction, both the equilibrium constants for binding and the dissociation rates for a soluble drug-protein complex can be measured [190–193,345–347]. Other techniques for binding and kinetic studies have also appeared because of efforts made in affinity chromatography. Important examples are modern biosensor platforms based on surface plasmon resonance (SPR) spectroscopy, in which binding of a solute with an immobilized agent is examined within a flow-based chamber rather than at the outlet of the system [14,343,348].

7. Conclusion

Over the last 50 years, affinity chromatography has emerged as a powerful and popular tool for obtaining highly selective separations. The initial growth of this method in the late 1960s and early 1970s was mainly driven by the creation of supports and immobilization methods that made it convenient to employ this method with natural binding agents for the purification of enzymes, antibodies, antigens, and other substances found in biological matrices. This was soon followed by the creation of methods that used non-biological binding agents, as well as additional supports and immobilization schemes, to expand the scope of affinity separations. Fields that now use this method range from biochemistry and molecular biology to biotechnology, analytical chemistry, pharmaceutical science, and biophysics.

This variety of applications is a result of the many advantages that are offered by affinity chromatography. One advantage, as illustrated in this review, is the wide range of binding agents that can be used in this technique [1–5]. Another key advantage is the highly selective nature of this separation method. This selectivity is a result of the specific interactions that are naturally present between many biological binding agents and their targets [1–7]. The strong binding that is often present in these processes allows many affinity-based separations to be carried out quickly and in only a few steps [1,4].

However, there are several factors that must be considered to obtain a successful separation in affinity chromatography. For instance, it is necessary to immobilize the binding agent onto or within a chromatographic support [1–6]. The immobilization process should ideally create a stable affinity ligand without significantly altering the binding properties of this ligand [43,79,80]. Another possible limitation of affinity chromatography is that biological agents such as antibodies are more expensive than stationary phases that are used in other forms of liquid chromatography [100,101]. This difference in price is partly offset by the fact that many affinity columns can be smaller than columns used in other types of liquid chromatography [1,4], and is of less concern when using non-biological ligands such as biomimetic dyes [126,127]. If the affinity column is to be reused for multiple cycles, care must also be taken to select application and elution conditions that allow both effective dissociation of retained targets and good column regeneration without permanently damaging the binding agent [8]. These issues represent areas of ongoing research and development in affinity chromatography. Continued growth is expected in the future for affinity chromatography as further advances are made in the binding agents, supports, immobilization schemes, and potential applications for this technique.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Affinity chromatography is an important tool for selective biochemical separations
- This method uses a biologically-related binding agent as the stationary phase
- A literature survey is made of trends in this field over the past 50 years
- The principles, history, and applications of affinity chromatography are discussed
- Supports, coupling methods, and binding agents for this method are summarized

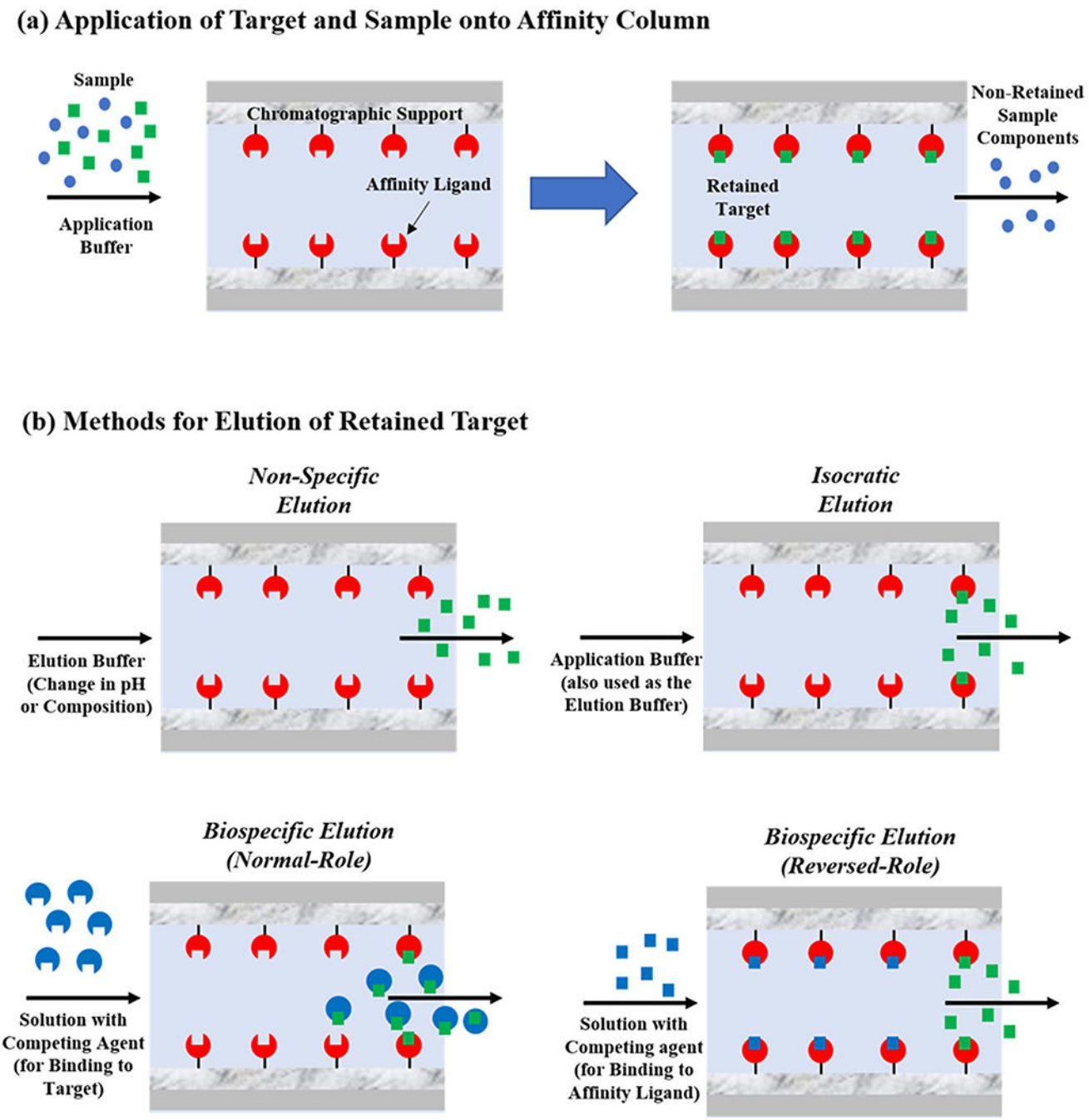

Figure 1.

The (a) sample application/washing steps and (b) examples of elution methods that are used the on/off mode of affinity chromatography. The three types of elution shown in (b) are non-specific elution, isocratic elution, and biospecific elution. Methods for biospecific elution can be further divided into normal-role elution, in which a competing agent binds to the target, and reversed-role elution, in which the competing agent binds to the immobilized affinity ligand.

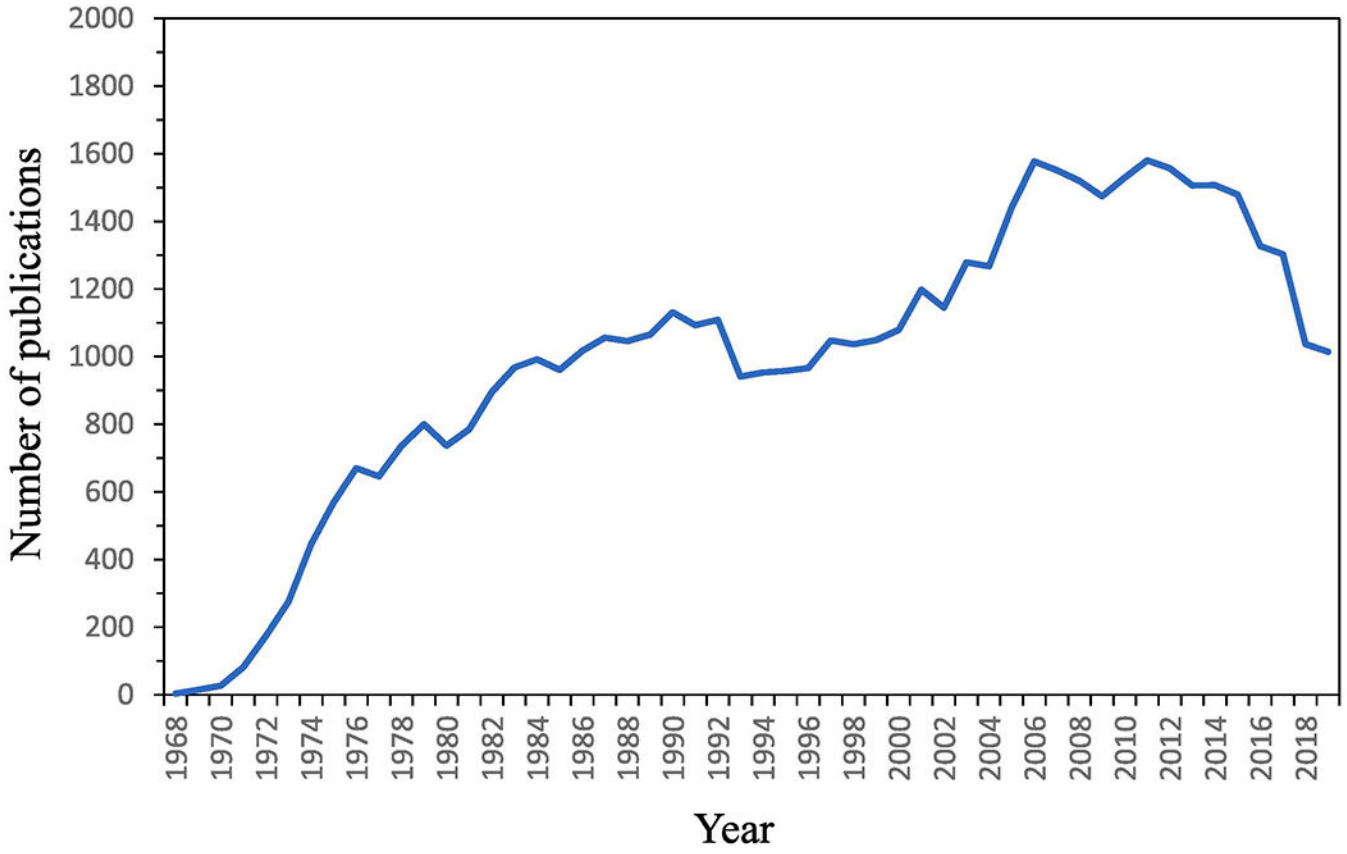

Figure 2.

Number of publications including the phrase “affinity chromatography” and that appeared between 1968 and 2019. These data were obtained through a search that was conducted in May 2019 using SciFinder. Similar trends, but with approximately twice the number of papers, were seen when a search was conducted for papers that included the concept of “affinity chromatography” (see Supplementary Material).

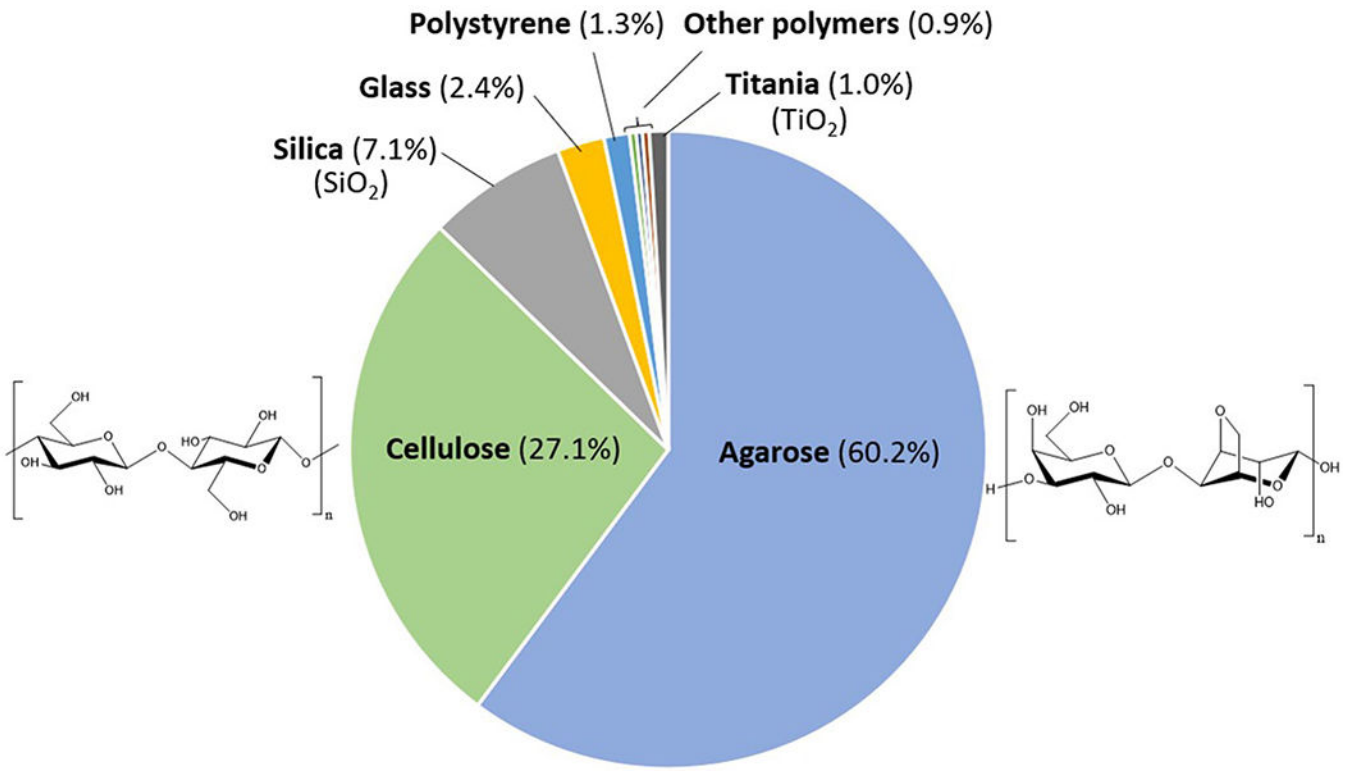

Figure 3.

Use of various supports in affinity chromatography, based on a search of papers that have employed this method. This search was conducted in May 2020 using SciFinder and examining papers that appeared between 1968 and 2019 with the phrase “affinity chromatography” used in close association with a particular support. Similar trends to those shown in this plot were seen when the given support and phrase “affinity chromatography” appeared in the same paper but were not necessarily closely associated with each other (see Supplementary Material). The group listed here as “other polymers” included polymethacrylate (used in 0.3% of the papers), polysulfone (0.3%), and polyamide (0.4%). The general structures or chemical formulas for agarose, cellulose, silica, and titania are included for reference.

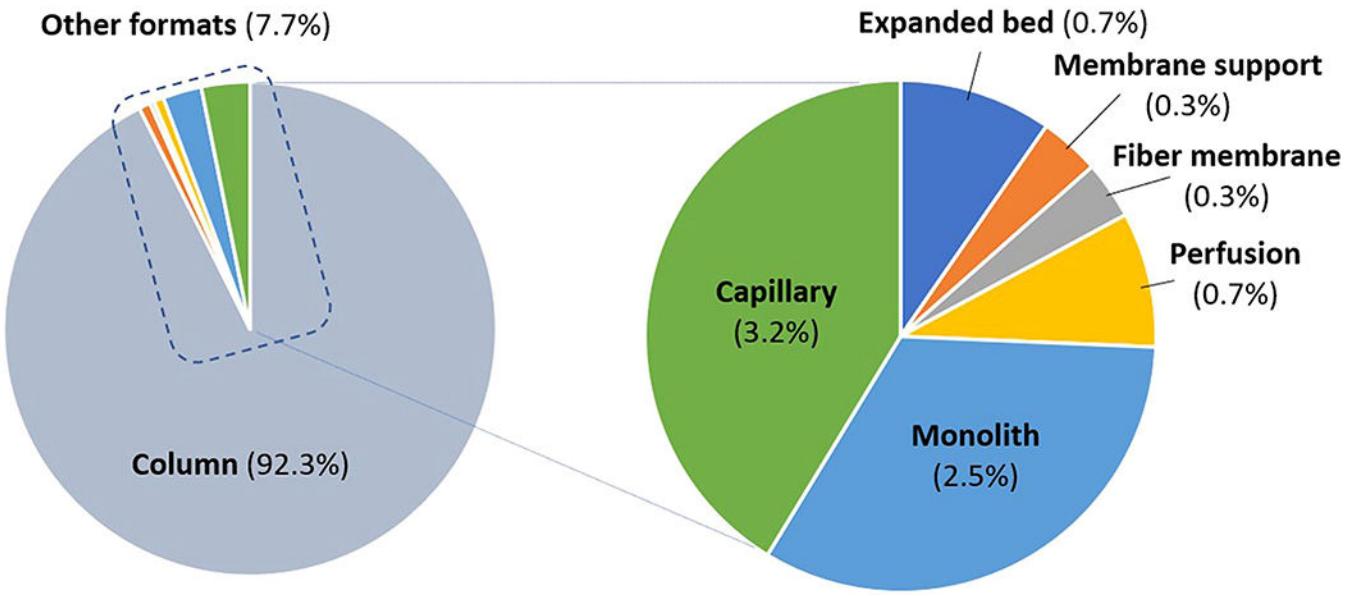

Figure 4.

Use of various support formats in affinity chromatography, based on a search of papers that have employed this method. This search was conducted in May 2020 using SciFinder and examining papers that appeared between 1968 and 2019 with the phrase “affinity chromatography” used in close association with a particular support format. Similar trends to those shown in this plot were seen when the given format for the support and phrase “affinity chromatography” appeared in the same paper but were not necessarily closely associated with each other (see Supplementary Material).

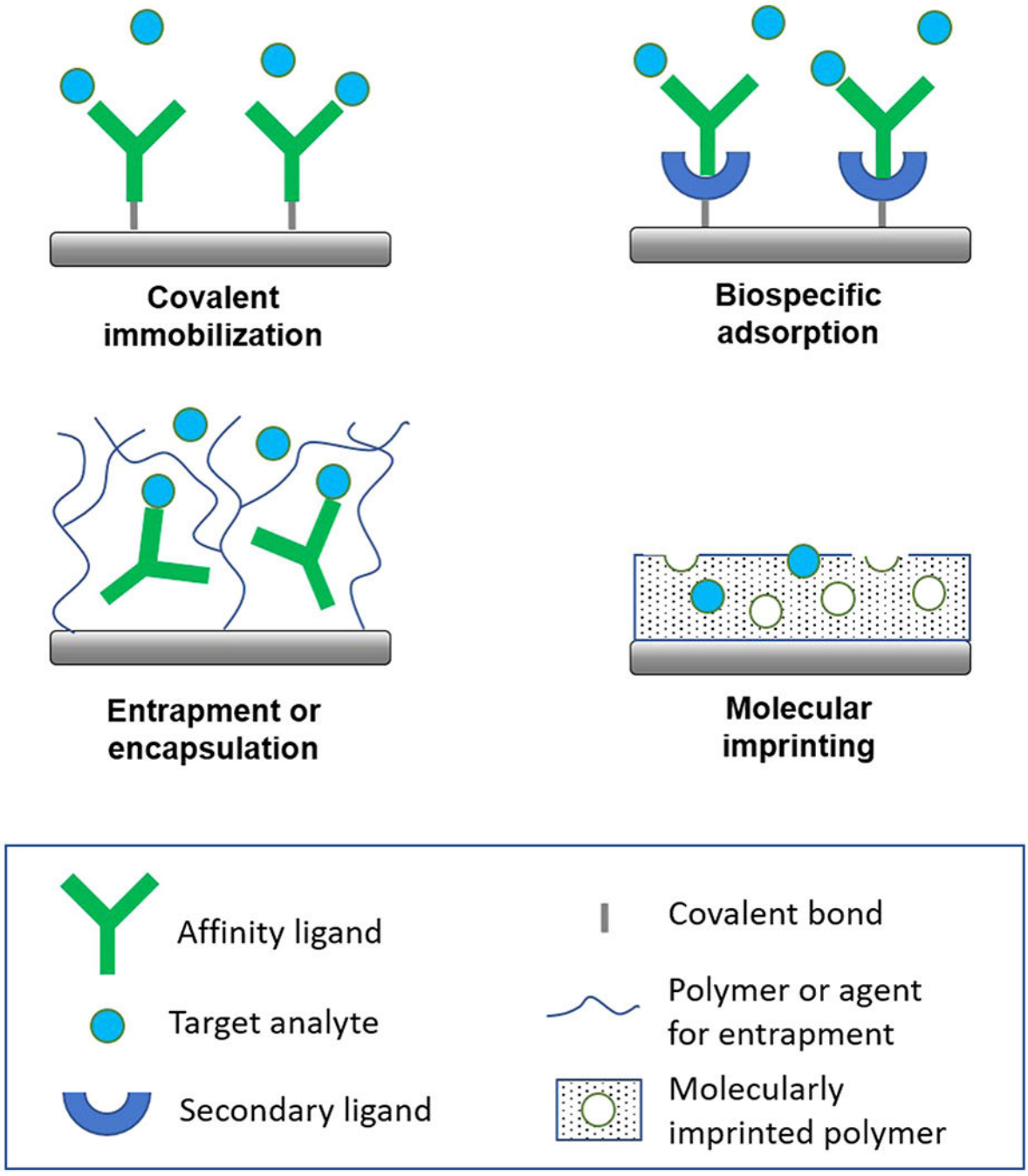

Figure 5.
Examples of general strategies that may be used to immobilize or place a binding agent, or affinity ligand, within a support for use as a stationary phase in affinity chromatography.

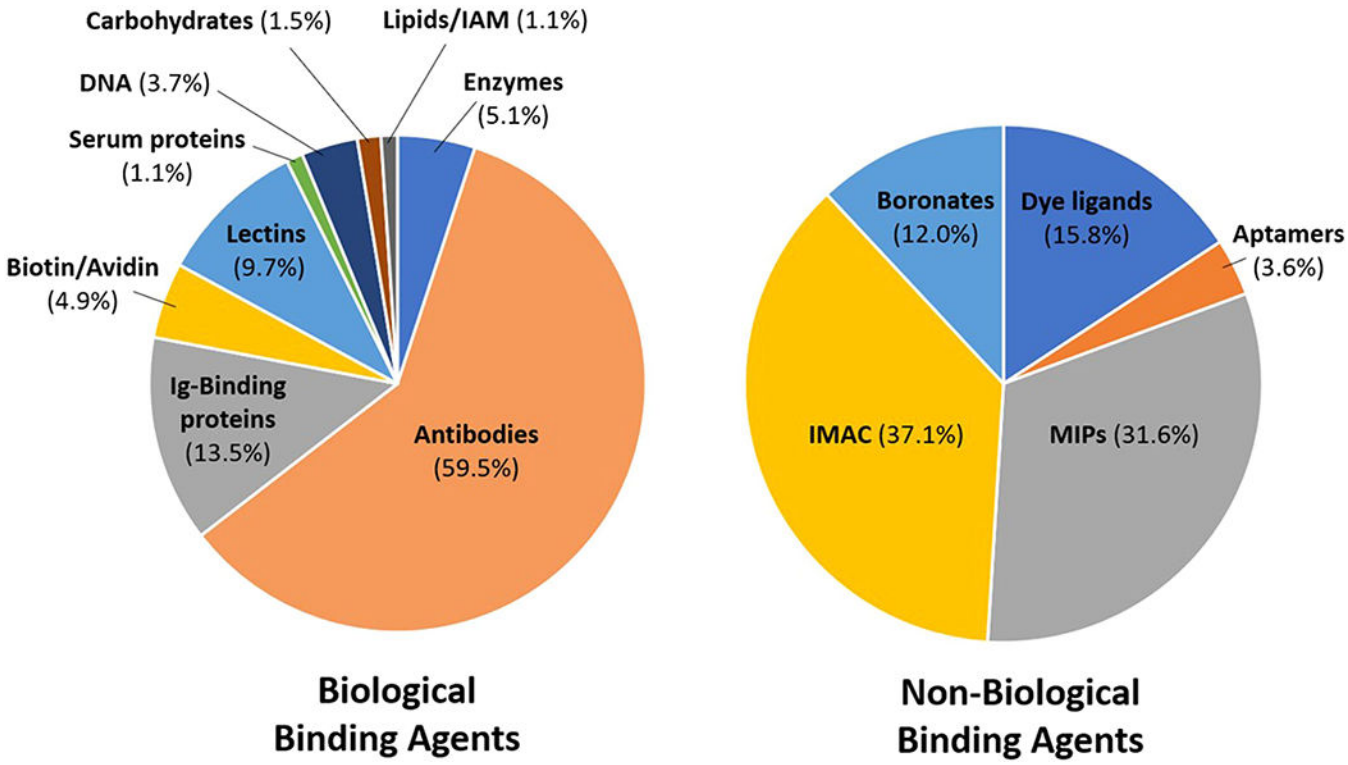

Figure 6.

Extent of use of representative biological and non-biological binding agents in affinity chromatography, based on a search of papers that have employed these agents. This search was conducted in June 2020 using SciFinder and examining papers that appeared between 1968 and 2020 with the phrase “affinity chromatography” or “chromatography” used in close association with the given type of binding agent. The plot on the left includes the results from 10,521 papers, and the plot of the right is based on 7,516 papers. Abbreviations: Ig, immunoglobulin; IMAC, immobilized metal-ion affinity chromatography; MIPs, molecularly imprinted polymers; IAM, immobilized artificial membrane.

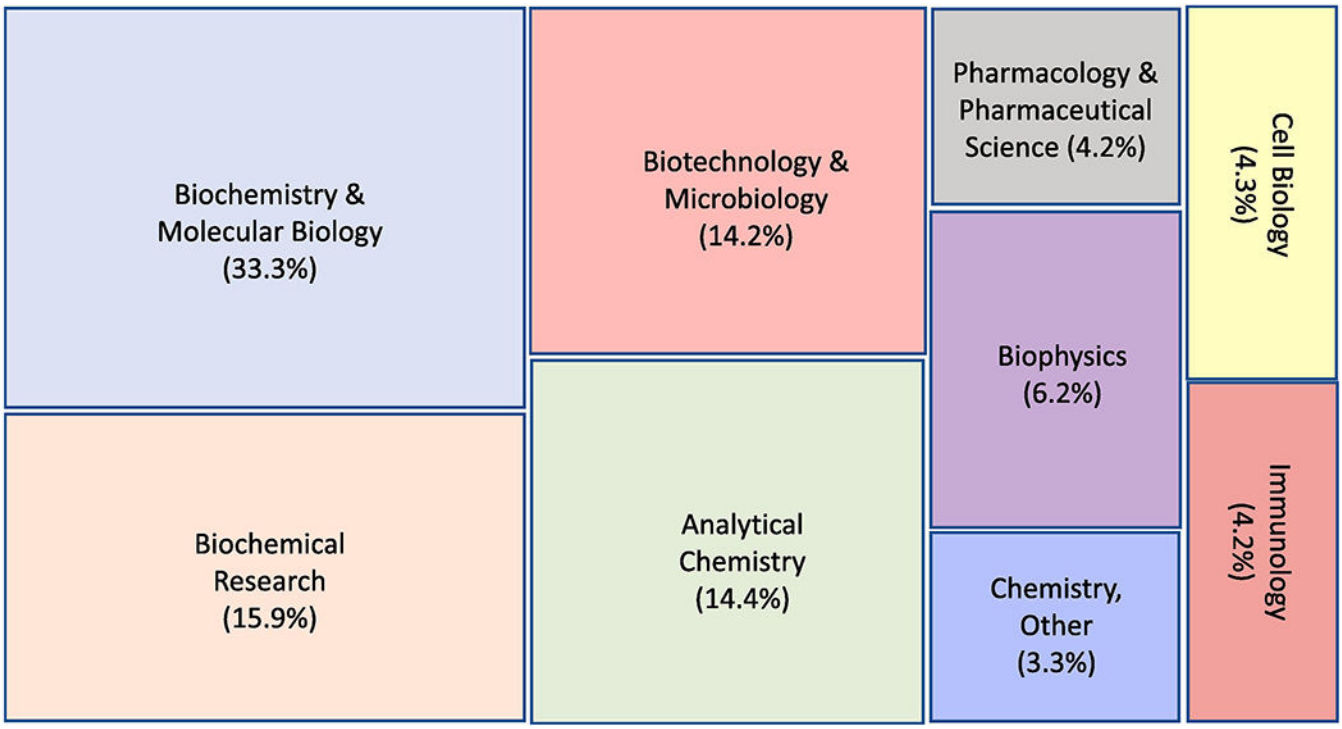

Figure 7.

Fields in which affinity chromatography is often used in chemical or biochemical separations, isolation, analysis, or characterization. These results are based on a literature search made using SciFinder during January 2019 for areas with papers in the listed fields that were linked to the term “affinity chromatography”. The percentages shown in this graph are based on a total of 46,335 papers that were obtained during this search.